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AN INTERNATIONAL JOURNAL REPORTING THE PRACTICAL APPLICATION OF OUR NEWER KNOWLEDGE OF NUTRITION

CONTENTS

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The Journal of Clinical Nutrition

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VITAMIN A *in* RHEUMATIC FEVER

By A. L. JACOBS, M.A., B.M., M.R.C.P., Z. A. LEITNER, M.D., T. MOORE, SC.D., AND I. M. SHARMAN, PH.D., F.R.I.C.

INTEREST in the significance of vitamin A status in rheumatic fever has been aroused by investigations by Coburn and other workers, and has followed two distinct lines of development. Firstly, it has been suggested that deficiency of vitamin A, and other forms of malnutrition, may be among the conditioning factors which cause a small proportion of patients with streptococcal infection of the throat to develop rheumatic fever. In support of this claim there is evidence that a good diet may reduce the incidence or rate of recurrence of rheumatic fever in children, although there has been no clear demonstration that special importance should be attached to vitamin A.[1,2] Secondly, it has been shown that in rheumatic fever the metabolism of vitamin A is abnormal, as indicated by its greatly reduced level in the blood plasma.[3] Again, the question arises whether special attention should be paid to this abnormality, since other metabolites are certainly affected. Harris *et al.*,[4] for example, have shown that in acute rheumatic fever the excretion of vitamin C is greatly diminished. Rheumatic fever, moreover, is not unique in reducing the concentration of vitamin A in the plasma; the level tends to fall in pyrexia of any origin.[5]

These considerations make it difficult to decide whether vitamin A plays an active part in supporting the body's resistance to rheumatic fever, or whether it merely suffers unspecific side effects in common with many other metabolites. Even if the second alternative should prove correct, however, the severity of the losses of vitamin A which are sustained clearly deserves study. Recovery from a single short period of pyrexia is usually accompanied by a prompt return of the plasma vitamin A to within normal limits, the vitamin presumably being mobilised from the large reserves stored in the liver. It might be considered, therefore, that after recovery from rheumatic fever the vitamin A status might well be left alone to correct itself. It must be borne in mind, however, that attacks of this disease tend to recur, and that even if cardiac complications are avoided the period of convalescence is often prolonged. In face of such sustained demands, even the substantial reserves originally present in the liver might eventually prove inadequate. It was thought desirable, therefore, to investigate the levels of vitamin A and carotenoids in the blood plasma of patients at various stages during and after acute rheumatic fever, and to relate the values obtained with data for body temperature and erythrocyte sedimentation rate (E.S.R.). For purposes of comparison, similar observations have also been made in patients with certain other diseases.

Earlier data at our disposal on the vitamin A reserves of the liver have been searched for information on the vitamin A reserves present

From the Whittington Hospital, London, and the Dunn Nutritional Laboratory, University of Cambridge and Medical Research Council.

at autopsy in the livers of subjects who had died from heart diseases which were presumably of rheumatic origin.

Experimental

Material and Methods

Serial specimens of blood plasma from patients with rheumatic fever, and from patients with certain other diseases, for purposes of comparison, were obtained during the years 1945–48 from Paddington Hospital and the Whittington Hospital, London. The patients with rheumatic fever were given sodium salicylate during the acute stage in doses ranging from 6 to 10 Gm. daily, according to the severity of the condition and age of the patient. As the clinical condition improved the dosage was reduced, but a maintenance dose of 3–4 Gm. daily was given for at least 3–4 weeks after complete disappearance of all clinical symptoms and signs. During the whole period of illness the patients had ordinary hospital diet with a liberal allowance of milk.

Vitamin A and carotenoids were estimated by a modification of Kimble's[6] method, with correction for the contribution of carotenoids to the antimony trichloride reaction.

The effects of disease on the vitamin A and carotenoid contents of the plasma were measured by comparison with normal values reported by Moore and Leitner.[7] In confirmation of general experience, a wide range of values was found for both substances in healthy adults and in hospital patients with diseases not known to affect their vitamin A metabolism. The average vitamin A for mixed sexes in the London area was assessed at 120 I.U. per 100 ml. and total carotenoids at 150 "I.U." (0.6 μg. units without reference to biological activity).

The Plasma Vitamin A and Carotene in Relation to Body Temperature

In Table I the average levels of vitamin A and carotenoids found in 100 patients with acute rheumatism have been arranged according to arbitrary ranges of body temperature. The patients examined were equally divided in sex, and ranged in age from 5 to 60 years, with an average of 20.5 years and with 64 per cent of the patients between the ages of 5 and 19 years. It will be seen that the levels of vitamin A were reduced at raised body temperatures. This reduction was found in the temperature range 98.9–100°, and in acute

TABLE I

Carotenoids, Vitamin A and E.S.R. in Relation to Body Temperature. Patients from Hospitals in Paddington and Archway Group

Temperature Range	No. estimations	Carotenoids	Vitamin A	E.S.R.
°F.		I.U./100 ml.	I.U./100 ml.	mm./hr.
Acute rheumatism (100):*				
Below 98.0	170	105	105	17.7
98.0–98.8	381	104	104	22.6
98.9–100.0	44	113	74	53.5
Over 100	28	71	50	83.6
Pneumonia (21):				
Below 98.0	12	91	88	20.0
98.0–98.8	27	97	98	25.7
98.9–100.0	13	90	65	51.8
Over 100	2	152	34	—
"Subacute rheumatism" (20):				
Below 98.0	22	109	119	16.2
98.0–98.8	48	117	100	11.9
98.9–100.0	10	113	118	13.7
Over 100	1	60	90	13
Pleural effusion (22):				
Below 98.0	24	97	97	24.5
98.0–98.8	52	130	86	34.8
98.9–100.0	20	136	73	40.0
Over 100	9	103	55	52.9
Rheumatoid arthritis (16):				
Below 98.0	36	116	103	49.4
98.0–98.8	59	109	96	59.7
98.9–100.0	11	77	67	79.0
Over 100	5	72	49	106.0
Erythema nodosum (12):				
Below 98.0	9	136	112	15.1
98.0–98.8	18	120	104	31.5
98.9–100.0	7	87	68	55.5
Over 100	0	—	—	—
Acute tonsillitis (18):				
Below 98.0	5	141	108	9.5
98.0–98.8	19	128	88	10.1
98.9–100.0	6	124	63	25.7
Over 100	2	103	58	32.5

* Figures in parentheses indicate the number of patients in each group.

rheumatism a further reduction was observed at temperatures of over 100°. In the other diseases, in which the patients examined were of both sexes but not necessarily in equal numbers, the average values for vitamin A also tended to fall as the range of body temperature was increased.

	No. estimations	Carotenoids	Vitamin A	E.S.R.
		I.U./100 ml.	I.U./100 ml.	mm./hr.
Acute rheumatism:				
Below 98°	170	. 105	105	18
98.0–98.4°	338	103	103	22
Above 98.4°	113	89	76	50

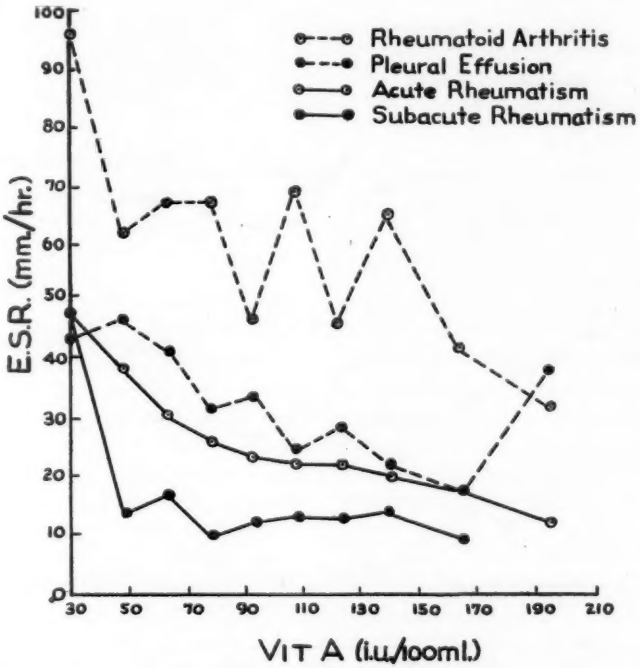

Fig. 1. E.S.R.—Vitamin A curves

Carotenoid levels tended to respond less noticeably to temperature increases. In the range 98.9–100° reduced levels were found only in rheumatoid arthritis and erythema nodosum. At temperatures of over 100°, however, carotenoids were reduced in acute rheumatism. It will be noticed that even at normal temperatures the carotenoid levels remained below those found in health.

In choosing the arbitrary ranges of temperature shown in Table I the main purpose was to demonstrate the relation between temperature and vitamin A. The ranges taken, however, are obviously less appropriate as a guide to rheumatic activity, and on Dr. B. E. Schlesinger's advice our data may for this purpose be rearranged as follows:

Vitamin A in Relation to E.S.R.

Mean values for E.S.R. at the various temperature intervals are included in Table I. The data were also regrouped according to arbitrary vitamin A ranges, and the corresponding mean E.S.R.'s calculated. These are shown in graphical form in Figure 1. In each disease a tendency for vitamin A to fall with increasing E.S.R. was observed, as might be expected from the association between E.S.R. and body temperature. At corresponding vitamin A levels the E.S.R., however, was much higher in rheumatoid arthritis than in acute rheumatism, subacute rheumatism and pleural effusion. This observation is in accordance with the well-known tendency for

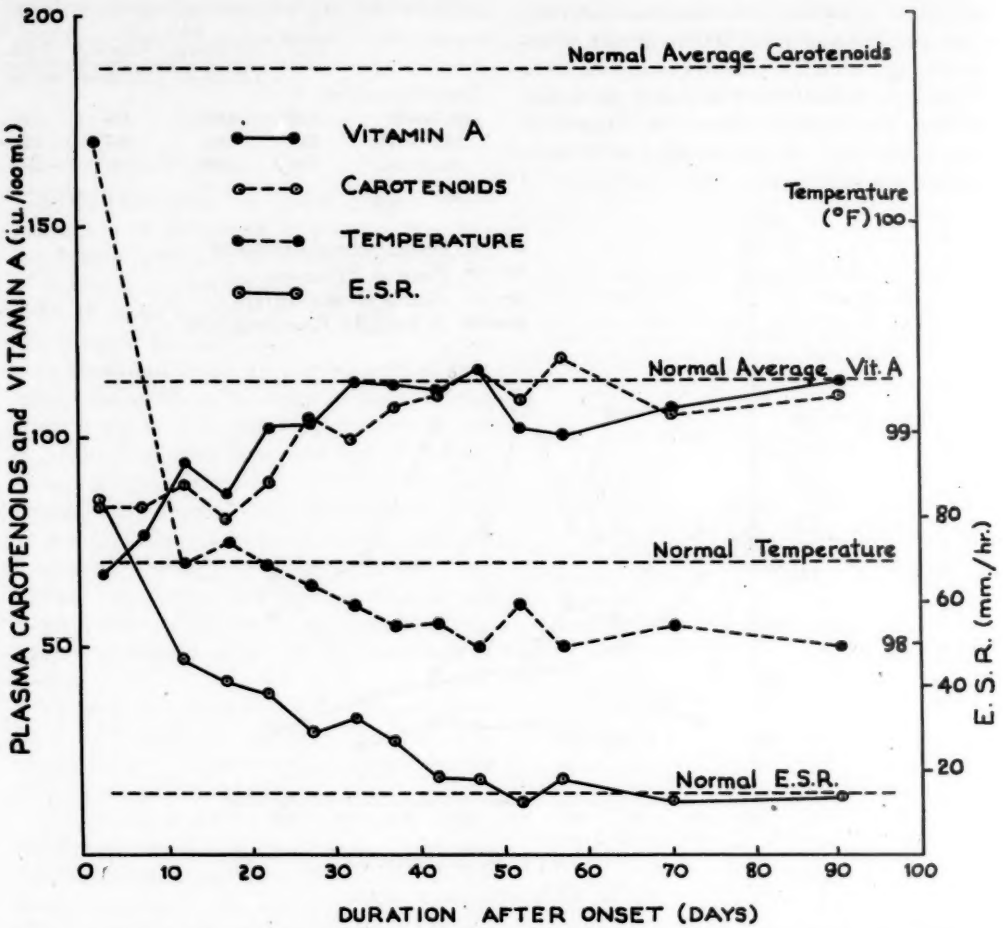

Fig. 2. Changes in vitamin A, carotenoids, body temperature, and E.S.R. in patients (100) recovering from acute rheumatism

the E.S.R. to be high in rheumatoid arthritis, even in the absence of pyrexia.

Changes in Vitamin A, Carotenoids, Temperature, and E.S.R. in Relation to the Time after the Inception of Rheumatic Fever

Figure 2 was obtained by arranging data for the 100 rheumatic fever cases according to the time after the inception of the disease at which the observations were made. It will be seen that the mean temperature returned to normal after 2–3 weeks, and was afterwards subnormal. Vitamin A rose, and the E.S.R. fell, with decreasing rapidity in the later stages of recovery, until after 7 weeks the levels in each instance were almost normal.

Total carotenoids showed increases parallel to those in vitamin A, but the maximum levels reached remained well below the normal average. A similar degree of subnormality, however, was observed in nonfebrile patients suffering from other diseases.

VITAMIN A IN THE PLASMA OF PATIENTS SHORTLY BEFORE DEATH

The data so far presented have indicated that the mean vitamin A for large numbers of patients falls when the body temperature

TABLE II

Fatal Cases Showing Low Premortal Vitamin A Values

Patient	Age	Disease or cause of death	Days before death	Temperature	E.S.R.	Carotenoids	Vitamin A
				° F.	mm./hr.	I.U./100 ml.	I.U./100 ml.
A. B.	59	Carcinoma bronchi	25	98	10	42	80
A. F.	37	Femoral thrombosis (embolic lung abscess)	14	98	53	43	43
S. J.	59	Syphilitic aortitis	13	?	—	46	54
J. S.	21	Mitral stenosis congestive failure (rheumatic origin)	12	97.2	6	68	29
G. B.	69	Pyogenic arthritis	12	97.6	72	55	28
E. B.	34	Uraemia	9	?	—	79	49
H. B.	23	Pneumonia, congestive heart failure	6	97.8	18	65	13
F. M.	10	Chronic rheumatism. Dyspnoea. Lung collapse	5	97	68	144	64
C. H.	52	Acute rheumatism	5	99	98	36	21
Mean	40		11	—	—	64	42

rises. It must be emphasised, however, that this inverse relationship did not always hold good in individual patients, in many of whom inconsistent changes were observed. These irregularities were seen in many patients who eventually recovered, but a low level of vitamin A without elevated body temperature occurred with noticeable frequency in patients examined shortly before death. Data were collected from only one such patient with acute rheumatism and from two others with diseases which were presumably of rheumatic origin, and in Table II additional data have been added which relate to patients who died from other diseases, and from whom specimens were received during the period while the present investigation was proceeding. The values given are the last observed before death. It will be seen that low levels were invariably found, although the body temperatures were usually normal or subnormal.

The Vitamin A Reserves of the Liver in Fatal Cases of Juvenile Heart Disease

No specimens of liver were taken from patients who died in the present investigations. It may be of interest, however, to record the individual values found by Ellison and Moore (1937) in children who had died from heart diseases, mostly of rheumatic origin. From Table III it will be seen that the range of values found in heart disease, with a mean of 28 I.U. per Gm., was much lower than in accidental death, mean of 129 I. U.

Moore (1937) also examined the vitamin A contents of the liver in adults dying of heart disease, and found that vitamin A was completely or almost absent in 20 per cent of the patients with valvular lesions.

Discussion

The present observations confirm and extend previous findings that the metabolism of vitamin A is disturbed in rheumatic fever. It remains difficult, however, to decide how far the vitamin need be taken into account in explaining the progress of the disease, or in planning treatment. Obviously there are many possibilities to be considered beyond the simple conception that dietary deficiency of the vitamin may reduce resistance to the disease. Thus the disease may cause a reduced consumption of food containing the vitamin, or may interfere with the absorption of the vitamin from such food as is consumed. A conditioned deficiency can thus be visualised which might reduce resistance to the further progress of the disease. Possibly the rate of expenditure of the vitamin in the tissues may be increased, and the stores present in the liver may be immobilised by failure of the regulatory mechanism which releases the vitamin into the blood. Without attempting to discriminate

TABLE III

Vitamin A Reserves in the Livers of Children Dying from Heart Disease, as Compared with Those Found in Accidental Death

	Name	Sex	Age	Place	Post-mortem report	Vitamin A
						I.U./Gm. liver
Heart cases	CW	M	13	L	Simple endocarditis	0
	AL	F	11	B	Congenital heart disease	3
	MP	F	12	G	Subacute rheumatic endocarditis	3
	GGS	M	6	L	Rheumatic endocarditis	9
	JEM	F	8	L	Rheumatic heart disease	12
	JR	M	14	G	Chronic rheumatic endocarditis	23
	JC	M	14	G	Rheumatic endocarditis	37
	CN	M	7	B	Acute rheumatism and rheumatic carditis	60
	SM	F	4/12	B	Rheumatic carditis	105
					Mean	28
Accident cases	EM	M	7	G	Fractured skull	3
	FM	F	3	G	Fractured skull. Meningitis	15
	MH	F	12	B	Ruptured spleen	30
	MP	F	1 6/12	G	Lysol burn	75
	RN	M	4	Lo	Fractured skull	87
	GE	M	3	G	Burns	150
	WM	M	7	G	Fractured pelvis	150
	CF	F	7	G	Fractured skull	150
	IM	F	6	G	Fractured skull	150
	TS	M	11	G	Fractured skull	150
	DC	M	5	G	Fractured skull	300
	MO	F	7/12	?	Burns	300
					Mean	129

B = Belfast, G = Glasgow, L = Leeds, Lo = London.

between these possibilities, however, it is clear that in acute rheumatic fever the level of vitamin A in the plasma is reduced, while in chronic heart disease of rheumatic origin the liver reserves of vitamin A often reach vanishing point.

The prescription of diets in convalescence from rheumatic fever should obviously be based on the assumption that the metabolism of many nutrients may be affected, and dosing with vitamins should not be considered an effective substitute for nutritious and appetising food. In view of the clear evidence that vitamin A metabolism is affected, however, it would seem a reasonable insurance to provide halibut liver oil, or some other potent concentrate, at a dose providing an intake considerably in excess of the adult's requirement of 2500 I.U. per day. Doses of 40,000–50,000 I.U. would appear to be reasonable.

Summary

(1) Vitamin A was estimated in the blood plasma of 100 patients with rheumatic fever, and the results were averaged according to arbitrary ranges of body temperature, or according to the time after the commencement of the disease.

(2) Vitamin A was considerably reduced during the febrile stage of the disease, but equally severe reductions were found in smaller groups of patients with pneumonia, pleural effusion, rheumatoid arthritis, erythema nodosum or acute tonsillitis.

(3) During convalescence the mean body temperature first reached normal, followed by vitamin A and by E.S.R.

(4) The changes in the mean carotenoid contents of the plasma were less clear-cut than those in vitamin A, but there was a consider-

able reduction when the body temperature exceeded 100°.

(5) The inverse relation between body temperature and vitamin A was not always observed in individual cases. Very low vitamin A values were found in specimens collected from nonfebrile patients with various diseases within 14 days of death.

(6) A re-examination of earlier data indicated that the vitamin A reserves found in the livers of children who had died from heart diseases, mainly rheumatic in origin, were much lower than in children who had died by accident.

(7) No claim can be made either that rheumatic fever differs from other febrile diseases in its effect on vitamin A metabolism, or that vitamin A is the only nutrient affected. The danger that the prolonged course of rheumatic fever may eventually exhaust the vitamin A reserves in the liver, and so produce a conditioned deficiency of vitamin A, should not, however, be ignored.

ACKNOWLEDGEMENTS

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RESUMEN

Vitamina A en la fiebre reumática

Se determinó la vitamina A en el plasma sanguíneo de 100 pacientes afectos de fiebre reumática, y de las cifras resultantes se sacaron promedios basados o en límites arbitrarios de temperatura corporal o en tiempo trascurrido desde el aparecer de la condición.

La vitamina A fué notablemente reducida durante el período febril de la enfermedad, pero unas reducciones igualmente severas se notaron en grupos menores de pacientes afectos de neumonía, efusión pleural, artritis reumatoide, *erythema nodosum*, o angina tonsilar aguda.

Durante la convalescencia el promedio de la temperatura corporal alcanzó por primera vez lo normal, seguido por la normalización de la vitamina A y de la velocidad de sedimentación globular.

Las alteraciones en el contenido promedio de los carotenoides del plasma fueron menos claras que las de la vitamina A, pero hubo una notable disminución cuando la temperatura corporal excedió de 100 grados.

La relación inversa entre temperatura corporal y vitamina A no siempre se observó en casos individuales. Muy pocos valores bajos de vitamina A se hallaron en las muestras obtenidas de pacientes no febriles con diversas enfermedades durante los 14 días antes de su fallecimiento.

Una nueva examinación de hallazgos anteriores indicó que las reservas de vitamina A en los hígados de niños muertos de cardiopatías, las más de origen reumático, fueron muy inferiores a las de niños muertos de accidentes.

No se puede pretender que la fiebre reumática difiera de otras enfermedades febriles en cuanto a su efecto sobre el metabolismo de la vitamina A, ni que la vitamina A sea el único factor nutricional afectado. Hay que no olvidar, sin embargo, el peligro de que el curso prolongado de la fiebre reumática pueda al fín agotar las reservas hepáticas de vitamina A y así conducir a una deficiencia condicionada de vitamina A.

ABSORPTION *of* IRON *from the Gastrointestinal Tract*

By WILLIAM J. GRACE, M.D.,* RONALD K. DOIG, M.D.,† and HAROLD G. WOLFF, M.D.‡
With the Technical Assistance of DIANA WASSERMAN STEINHOUSE

THE ABSORPTION of iron from the upper gastrointestinal tract following large doses of iron produces a prompt and brisk rise in the level of the serum iron.[1-5] Currently it is said that ferrous salts are more readily absorbed than ferric salts[2-7] and that both are less readily absorbed from the gastrointestinal tract of persons with achlorhydria.[2,3,7,9] The presence of free hydrochloric acid is held to be necessary for the conversion of ferric to ferrous iron,[3,7] in which state the iron is absorbed, and to prevent the precipitation of insoluble and nonabsorbable ferric salts.[3,10] A pH of 5 of the gastric content is believed to be the critical level for the conversion of ferric to ferrous iron. The absorption of iron is through the mucosa of the stomach and duodenum[3,5,11] and this corresponds closely to the distribution of ferritin in the gut.[12] However, as a striking exception to part of this hypothesis, it should be emphasized that the absorption of iron from the gastrointestinal tract of persons having Addisonian pernicious anemia is often prompt and adequate.[2,13] More recent studies using the technique of determination of the absorption of radioactive iron from the stomach and upper gastrointestinal tract[6,8] also seem to indicate, but not conclusively, that ferrous iron is better absorbed than ferric.

In the original experiments which led Widdowson and McCance to suggest that there was a limited absorption of iron rather than a colonic excretion,[14,15] the path of iron metabolism was inferred from balance studies. Inferences on the absorption of iron have also been made on the basis of clinical trial, as quoted by Hahn[4] and Heath and Patek.[7] However, over the last several years two additional methods have been extensively used: the study of the serum iron level (as in refs. 1, 2, and 5) and the estimation of the amount of radioactive iron absorbed and appearing in the red cells (as in refs. 5, 6, 8, 11, 13, and 16). Yuile *et al.*[16] state that their results show there is no close relation between the total amount absorbed and the height of the serum iron after the test dose. However, in their results, there is a general trend that higher curves go with greater absorption; and there is little doubt that investigators studying serum levels felt that these rises were of some significance. In a parallel field of study, the comparison of tolerance curves with actual absorption shows that there is a useful general relation for protein,[17] and for fat and vitamin A.[17,18] The probable greater merit of the tolerance curve has been discussed by Althausen *et al.*[17] We have adhered to the view that the height of the curve does give an indication of the functional activity of the bowel involved and this relates to the total absorbed.

In this paper we are reporting studies on the absorption of iron in healthy subjects and in the subject "Tom," in whom the presence

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of a large gastric fistula afforded a unique opportunity.[19]

Method

The serum iron was determined by the method of Kitzes[20] modified to use orthophenanthroline as the color reagent. In our hands this method showed values of 80–125 μg. per 100 cc. in healthy individuals. Duplicates were run on all specimens and they agreed within 5 μg. per 100 cc. Serial determinations on the same person from day to day showed a variation which was within the range of laboratory error. Specimens of serum which were cloudy or lipemic were not utilized; similarly, all those in which the icteric index was over 8 were discarded. The total and free hydrochloric acid values of the gastric juice were determined by the usual method of titrating with $N/10$ sodium hydroxide solution using Topfer's reagent and phenolphthalein indicator. The pH of the gastric content was determined by the Beckman pH meter.

The iron tolerance test was performed as follows:

Iron in the amount of 2 mg. per Kg. was given to the subject after an overnight fast. Specimens of venous blood were withdrawn at the time of the test dose and hourly thereafter for four hours (the curve obtained is referred to as the "iron tolerance curve"). Such a test was performed in seven healthy physicians and laboratory personnel. The healthy subjects were repeatedly studied, and observations were included on the absorption of iron when a dose of 5 Gm. of sodium bicarbonate was given with the test dose of iron.

Since a large number of experiments were performed on the subject "Tom," the test was modified. The dose of iron was given at least three hours after his early morning meal (4–6 a.m.). Specimens of gastric juice were obtained prior to the introduction of iron and at half-hour intervals for two hours after the introduction of the iron. An initial blood sample was not obtained. Two hours after the iron was introduced into the stomach a specimen of venous blood was obtained for determination of the serum iron. This was taken as an index of the absorption of iron. On 26 occasions at the end of the two-hour period, the subject's stomach was emptied and the total iron remaining in the stomach was determined by an appropriate modification of the Kitzes method. Levels of pH of the gastric contents above 5 were not encountered spontaneously, so that in one group of experiments the free hydrochloric acid was neutralized with sodium bicarbonate. In these experiments, after the initial specimen of gastric juice had been obtained, 5 Gm. of sodium bicarbonate was placed in the stomach with the dose of iron. A second dose was introduced an hour later. This was adequate to maintain pH greater than 5 for two hours, and there was no titratable free acid.

TABLE I

Rise in Serum Iron Level (μg. per 100 cc.) in Two Hours Following Administration of 2 mg./Kg. Iron by Mouth

	Serum iron levels following similar dose of various iron preparations			
Subject	Ferric	Ferric + bicarb.	Ferrous	Ferrous + bicarb.
D.B.	8	18	27	30
	7		50	
			125	
			49	
			90	
			120	
M.G.	178	22	139	75
			69	
A.M.	35	14	115	65 N*
	63		70 N	72
P.C.	18	82	82	120
	0		80	
	25		75	
R.D.	30 N	30 N	70	30
	62 N		45	
			110	
C.R.	71 N	182	120	22
	30 N		112	
	67			
W.G.	135	65	56 N	126
	15 N		77	
Average	51	59	84	67
	53		79	

*N = nausea.

Results

(1) *Healthy Subjects*

When a series of "iron tolerance" tests were performed on several subjects, there was vari-

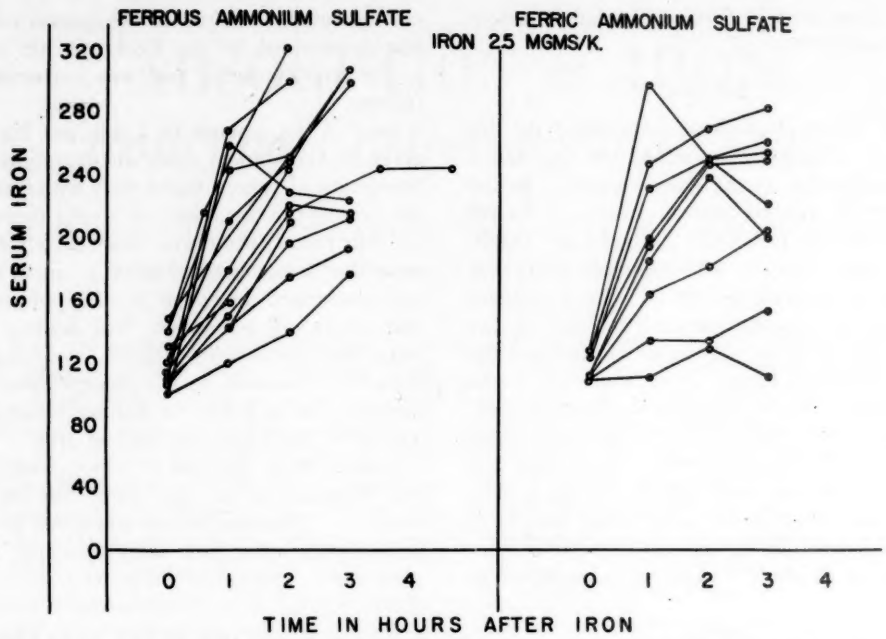

Fig. 1. Iron tolerance curves using ferrous and ferric ammonium sulfate in repeated observations on seven healthy subjects.

ation in the height of the tolerance curve from time to time (Table I and Fig. 1). When the levels of serum iron at two hours were compared, it was found that the level following ferrous iron was 192 μg. per cent; that following ferric iron was 166 μg. per cent; and no difference resulted from the simultaneous administration of bicarbonate (see Table I). This difference could be due to chance ($P = 7\%$). The same comparison (ferric versus ferrous), using the actual or calculated rise in serum iron level over two hours, showed a more significant difference ($P = 2\%$), the changes being 79 μg. and 53 μg. respectively. There were several experiments during which the subject complained of nausea. In such experiments, the serum iron change was less than when nausea was absent, and the slightly greater number of such low values when ferric iron was used accounted for a part of the difference between the two sets of results.

(2). Fistulous Subject

As in the healthy subjects, the absorption of iron varied widely from day to day (see Table II). There was no steady drop in the level of serum iron obtained as the experiments proceeded; that is, it did not appear that a saturation of the iron-absorbing capacity was occurring. There were lower values of the two-hour serum iron with ferric salts ($P = 4\%$). The two-hour serum iron levels were essentially the same when the pH of the gastric contents remained low, near pH 2, as when the pH stayed between 5 and 8 from the administration of sodium bicarbonate (Table III and Fig. 2). Only insignificant amounts of iron remained in the stomach at the end of two hours.

Comment

The data suggest that the absorption of iron is not related to the pH of the gastric contents. The findings in regard to the differential absorption of ferrous versus ferric iron indicate that ferrous iron is probably absorbed a little bit better than ferric iron. Although the difference is statistically important, the difference is certainly not very large and is probably not of clinical importance. It is most

TABLE II*

Date	2-hour serum iron	pH gastric juice: Before iron	½ hour after iron	1 hour after iron	1½ hours after iron	2 hours after iron
Ferrous Ammonium Sulfate						
10-29-52	185	2.1	—	2.6	—	—
10-30-52	257	1.4	1.8	1.3	1.7	—
10-31-52	185	1.2	1.8	1.5	1.8	—
11-3-52	195	1.0	1.5	1.4	—	—
11-12-52	175	1.4	1.2	1.2	1.3	—
11-14-52	156	1.3	2.1	1.7	—	—
11-17-52	132	1.7	1.8	2.2	2.3	—
11-24-52	147	1.7	6.2	1.1	6.8	—
11-25-52	140	1.3	3.3	2.9	6.0	—
11-26-52	235	1.5	5.9	3.5	2.2	—
12-1-52	90	1.8	6.7	7.4	7.9	—
12-10-52	223	6.3	5.7	8.5	6.8	6.6
12-11-52	185	5.1	5.4	5.4	7.2	—
12-12-52	175	8.2	7.3	6.3	7.0	—
Ferric Ammonium Sulfate						
11-6-52	145	1.5	1.4	1.5	—	—
11-10-52	150	1.2	1.4	1.5	1.5	—
11-13-52	125	1.5	1.3	1.2	—	—
12-3-52	160	2.8	2.1	3.7	5.1	—
12-4-52	130	1.7	2.6	7.2	7.5	—
12-8-52	145	1.6	2.4	7.4	8.3	—
12-9-52	215	—	—	—	—	—
12-15-52	155	8.2	6.4	2.6	4.2	—
12-17-52	210	7.1	7.0	7.6	—	—
12-18-52	160	7.6	6.6	8.3	7.2	—
12-19-52	200	7.1	7.9	8.6	7.9	—
12-22-52	187	6.3	7.0	8.9	8.3	—
12-23-52	92	8.0	6.5	8.4	7.9	—

* The 2-hour serum iron is the serum iron (μg. per 100 cc.) 2 hours after ingestion of 1 mg./Kg. of iron. All observations on same subject ("Tom"). The pH as measured by the photoelectric method is given in pH units at the stated time after the test dose of iron was administered.

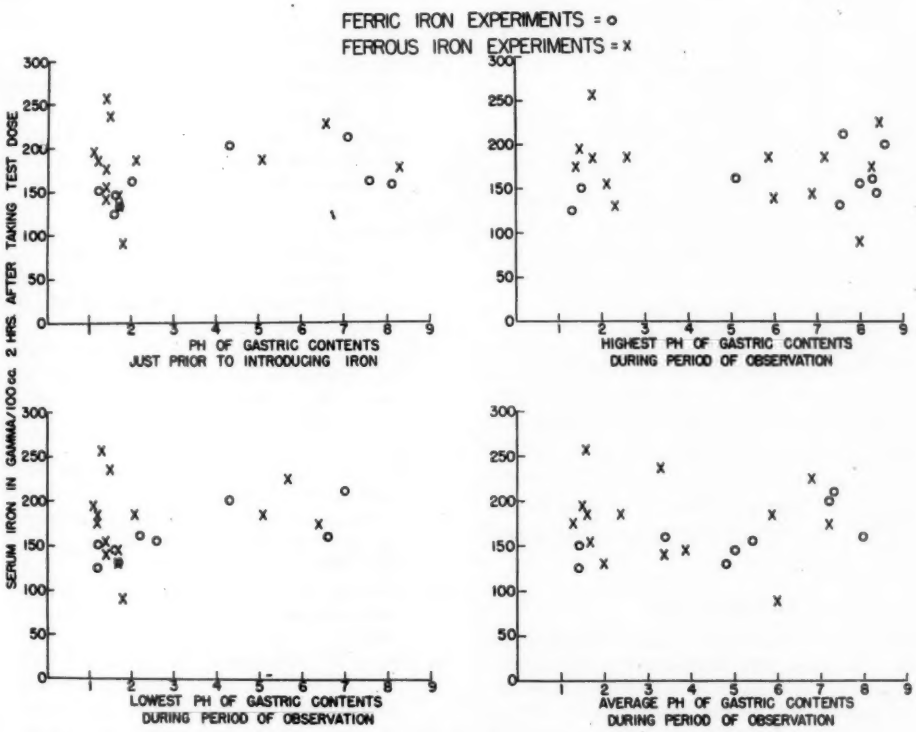

Figure 2.

likely that the failure to absorb iron is a manifestation of lowered absorptive capacity of the upper small intestine, rather than a defect in the hydrochloric acid secretion. An analogous situation is seen in sprue,[17] where the studies of the absorption of a great variety of substances show that a failure to absorb iron is included in the reduced absorptive capacity of the upper small intestine.

TABLE III

Serum Iron Level Two Hours After Administration of Iron to the Fistulous Subject, "Tom." Results in Each Column are in Chronological Order

	Ferrous iron	Ferrous iron plus bicarb.	Ferric iron	Ferric iron plus bicarb.
	185	223	145	155
	257	185	150	210
	185	175	125	160
	195	205	160	200
	175	177	130	187
	156	150	145	92
	132	—	215	—
	147	—	68	—
	140	—	63	—
	235	—	90	—
	90	—	103	—
	68	—	70	—
Average	164	186	122	167

In addition, a large proportion of the older age population are said to show no hydrochloric acid in their stomach, yet these people do not have a comparable amount of iron deficiency anemia.[21]

Summary

Iron-absorption studies were performed on a series of healthy persons and one subject with a gastric fistula. The data indicate that the absorption of iron is not necessarily related to the acidity of the stomach and that the absorption of iron is probably related to the absorptive capacity of the upper gastrointestinal tract.

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Resumen

Absorción del hierro del tracto gastrointestinal

Se realizaron estudios de la absorción del hierro en una serie de personas sanas y en un indivíduo con fístula gástrica. Los datos indican que la absorción de esta substancia no está necesariamente relacionada con el grado de acidéz estomacal y que más bien se encuentra en relación con la capacidad de absorción de la parte alta del tracto gastrointestinal.

Effects of VITAMIN E *Preparations on* PLASMA TOCOPHEROL *Levels*

By Ralph S. Overman, ph.d.,* Jane M. McNeely, m.s.,† Margaret E. Todd, b.s.,‡ and Irving S. Wright, m.d.§

The merits of *dl*-alpha-tocopherol as a therapeutic agent have been extensively investigated. Although work on the absorption of tocopherol, administered orally and parenterally, was reported by several groups of workers,[1-9] there still remains much to be learned about this subject. Therefore, the effects of various vitamin E preparations on plasma tocopherol levels were investigated, and the results obtained with different single and multiple doses by the oral route and with different single doses given parenterally are presented in this paper.

Experimental Methods

Procedure: Initially, an investigation of the daily and of the diurnal variations of plasma tocopherol levels was undertaken in subjects who had not received vitamin E preparations (Part I—Control Studies). Subsequently, the effects of single oral and parenteral administrations of several tocopherol compounds given in different doses and different forms were investigated (Part II—Single-Dose Studies). Finally, an investigation of the prolonged oral administration of *dl*-alpha tocopherol acetate given in different doses and different forms was carried out (Part III—Long-Term Studies).

The control studies comprised determinations of tocopherol levels repeated on ten successive days at 9:30 a.m. and of tocopherol levels repeated at various times of the day (9:30 a.m., 11:30 a.m., 1:30 p.m., and 3:30 p.m.). The single-dose studies comprised determinations of tocopherol levels initially and 2, 4, 6, 24 hours, and in some cases 48 and 72 hours after oral administration, and determinations of these levels initially and 2, 4, 6, 24, 48, and 72 hours after intramuscular administration of the vitamin E preparations. In the long-term studies the vitamin E preparations were given at 9:30 a.m. for twelve days and determinations of tocopherol levels were carried out just prior to ingestion of the drugs on the first, second, third, fourth, fifth, eighth, tenth, and twelfth days of the experiment.

Except for the study of the diurnal variation of plasma tocopherol levels for which ten subjects were used, each investigational phase comprised five subjects. All blood samples were nonfasting specimens.

Subjects: A total of 23 healthy, active adults, ranging in age from 26 to 36 years, were used for the study of plasma tocopherol levels without administration of vitamin E and of the absorption of the oral vitamin E preparations. All were on uncontrolled, self-

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chosen diets. The parenteral vitamin E preparations were administered to a total of 15 convalescing hospital patients, ranging in age from 40 to 60 years.

Analytical Method: Free tocopherol was measured by the spectrophotometric method of Quaife *et al.*[10] The method was adapted to the use of 2 to 3 ml. plasma instead of 0.06 ml. The optical density was measured in a 10 x 75 mm. cuvette with a Coleman Spectrophotometer Model No. 6A. The findings recorded in the tables are always the means of duplicate determinations.

*Preparations:** The following oral vitamin E preparations were used:

An aqueous emulsion of *dl*-alpha-tocopherol acetate, 100 mg./ml. (designated Form I)†

An aqueous emulsion of *dl*-alpha-tocopherol acetate, 100 mg./ml. (designated Form II)†

dl-alpha-tocopherol acetate capsules, 100 mg. (Ephynal acetate Capsules)

dl-alpha-tocopherol acetate tablets, 100 mg. (Ephynal acetate Tablets)

The parenteral vitamin E preparations tested were:

An aqueous emulsion of *dl*-alpha-tocopherol, 2 ml. ampuls, 50 mg./ml.

dl-alpha-tocopherol in sesame oil, 1 ml. ampuls, 100 mg./ml. (Ephynal).

dl-alpha-tocopherol monosodium phosphate, aqueous-isotonic, 2 ml. ampuls, 50 mg./ml. (Warren-Teed Products Company).

Statistical Methods

1. The duplicate determinations of the plasma tocopherol level for each plasma sample were averaged and thereafter treated as a single reading.

2. The five readings for the five different individuals taken under each set of circumstances were then averaged and the standard deviation and sometimes the standard error of the mean and the mean maximum rise and its standard deviation determined to facilitate the observation of relationships (see Tables I–V, VII).

3. A further analysis based on increase readings was also undertaken in the oral administration experiments. In the single-dose experiments the initial readings (9:30 A.M.) for each day of testing were subtracted from the 2, 4 and 6 hour readings for the same person for the same day and all computations thereafter were based on these increase (or decrease) readings rather than on the original values. This procedure was designed to eliminate the influence of changes from day to day in the individual's plasma level of tocopherol and to minimize differences between individuals. In the long-term experiments increases were computed in relation to the last morning reading prior to the administration of tocopherol.

4. The possibility that body weight might influence the response to a single oral dose was considered. The participants were therefore arranged in order of body weight and their corresponding increases at six hours examined. There appeared to be no correlation between body weight and vitamin E response. Weight was therefore ignored in the remaining analysis.

5. It was found that there was a significant difference among the individuals in their response to identical amounts of vitamin E. In other words, an individual was more consistent with himself in his degree of response to different amounts and various vitamin E preparations than he was with the responses of other individuals. In view of these findings, the procedure of pairing two different readings for the same individual was employed in order to represent the same subjects on both sides of the comparison. Thus the effect of differences among the individuals was minimized. For a given subject, a comparison was made of vitamin E levels obtained under similar conditions except for the variable being evaluated. The differences between paired readings in a given comparison were always

* Preparations were supplied by Dr. Leo A. Pirk, Department of Clinical Research, Hoffmann-La Roche, Inc., Nutley, N. J.

† For the Form I Tweens and for the Form II glyceryl monostearate, ascorbic palmitate and gelatin were used as emulsifying agents.

determined by subtracting in the same direction. Since comparable readings for a given individual were not always available for every variable evaluated, the total number of paired items varied from test to test.

6. All available pairings pertinent to a given comparison were assembled and considered in each test. Because of the small samples available subgroups of readings taken under diverse conditions of time, drug, and dosage were combined in so far as possible.*

7. Conclusions as to significance are based on the assumption that if there were no real differences between the groups compared, the minus and plus differences between pairs would balance and yield an average difference between pairs departing from zero no further than would be expected on a chance basis considering the standard error of the mean difference. Computations involved the calculation of the ratio of the actual mean difference between pairs to its standard error.

8. Analysis of variance methods were also used in certain generalized tests where appropriate.†

* Combinations of somewhat dissimilar data were considered permissible in the single-dose analysis since (1) each condition was equally represented on the two sides of the comparisons being made, (2) conversion of the readings to differences between paired increases improved greatly the homogeneity of the data, and (3) exploratory graphic and computational analysis of selected subsample combinations failed to demonstrate that in the case of the single-dose data, the use of combinations of subsamples in a single pairing analysis would violate significantly the basic assumptions of the statistical method adopted (namely, that the original observations were independent observations of a population of roughly normal distribution). The increases resulting from the repetition of similar doses for the same individual were averaged, however, before being paired, since tests indicated that they otherwise failed to meet this requirement of independence.

† The analysis of variance procedure could not be applied to the original data as an over-all inclusive method of analysis since individual differences could not then have been controlled (since the persons tested varied irregularly from subgroup to subgroup) and since the unpaired readings taken under the influence of varying doses of tocopherol failed even after transformation to meet the requirement of this method for homogeneity of variance within subsamples.

Results

PART I—CONTROL STUDIES

The plasma tocopherol levels studied for five normal individuals at 9:30 A.M. on each of ten successive days are recorded in Table I.

Plasma tocopherol levels determined at four different times during the day (9:30 A.M., 11:30 A.M., 1:30 P.M., and 3:30 P.M.) for ten normal subjects are recorded in Table II. The mean plasma tocopherol concentration thus studied at 9:30 A.M. on 50 plasma samples was *1.002* mg. per cent with a standard deviation of ± 0.254, and standard error of the mean ± 0.035. The range of values observed in this group was from 0.46 to 1.77 mg. per cent.

Difference Between Individuals

The tocopherol plasma levels of five different individuals at 9:30 A.M. on ten different days (Table I) were analyzed by the method of the analysis of variance. The mean tocopherol levels were found to differ more from each other than would be expected on a chance basis in view of the amount of day-to-day fluctuation in the same individual.* If these five individuals are representative of persons in general, differences between individuals are sufficient to warrant control of this factor in vitamin E studies. The pairing procedure used throughout the analysis is designed to equalize on both sides of all comparisons these differences between individuals.

Difference by Time of Day in Vitamin E Plasma Levels

The method of the analysis of variance was employed to determine whether the variation in means of the plasma vitamin E levels at four different times during one day exceeded to a significant degree the variation that would be anticipated between the same ten individuals at any given time of day. The variance of the time means was not found to be significantly greater (was, in fact, less) than would be expected on the basis of variation of plasma

* $F = 26.30$, whereas F at the 1 per cent level for the appropriate degrees of freedom equals 3.78.

TABLE I

Repeated Tocopherol Levels (mg. per cent) in Blood Plasma of Normal Controls—Samples Taken After Breakfast at 9:30 A.M.

Subject	Days 1	2	3	4	5	6	7	8	9	10	Mean	S. D. ±	S. E. ±
MJ	0.92	0.82	0.65	0.46	0.77	0.81	0.80	0.76	0.77	1.07	0.78	0.19	0.06
DO	1.12	1.25	1.21	1.28	1.77	1.63	1.37	1.60	1.50	1.58	1.43	0.22	0.07
RW	0.80	0.78	0.86	0.79	0.86	0.86	0.96	0.90	1.04	1.26	0.91	0.15	0.05
TM	0.90	0.87	0.80	0.91	0.85	0.86	0.91	0.98	1.04	1.25	0.94	0.13	0.04
DS	0.95	0.98	0.92	0.75	0.94	0.98	1.01	1.10	0.97	0.90	0.95	0.09	0.03
Mean	0.94	0.94	0.89	0.84	1.04	1.03	1.01	1.07	1.06	1.21			
S. D. ±	0.12	0.19	0.21	0.30	0.41	0.34	0.22	0.32	0.27	0.25			
S. E. ±	0.04	0.08	0.09	0.13	0.18	0.15	0.10	0.14	0.12	0.11			

TABLE II

Tocopherol Levels (mg. per cent) in Blood Plasma of Normal Controls at Various Times of the Day

Subject	Time of day 9:30 a.m.	11:30 a.m.	1:30 p.m.	3:30 p.m.	Mean	S. D. ±	S. E. ±
DS	0.95	0.93	0.86	0.87	0.90	0.04	0.02
RW	0.80	0.91	0.85	0.87	0.86	0.05	0.02
TM	0.90	0.83	0.89	0.91	0.88	0.03	0.02
MJ	0.92	0.78	0.84	0.82	0.84	0.06	0.03
DO	1.12	1.06	0.94	0.99	1.03	0.08	0.04
DH	1.03	0.98	1.08	1.07	1.04	0.05	0.02
DOL	1.02	0.96	1.07	1.08	1.03	0.06	0.03
DP	0.98	1.01	0.93	0.96	0.97	0.03	0.02
DF	1.01	1.01	1.06	1.01	1.02	0.03	0.01
DSc	0.96	0.94	0.95	0.80	0.91	0.08	0.04
Mean	0.97	0.94	0.95	0.94			
S. D. ±	0.09	0.09	0.09	0.10			
S. E. ±	0.03	0.03	0.03	0.03			

TABLE III

The Means[a] and Standard Deviations for Plasma Tocopherol Levels (mg. per cent) Following the Single Oral Administration of *dl*-alpha-tocopherol Acetate in Aqueous Emulsions and Capsule Forms

Hours	100 mg. Form I M.	S. D. ±	Form II M.	S. D. ±	Capsule M.	S. D. ±	200 mg. Form I M.	S. D. ±	Form II M.	S. D. ±	400 mg. Form I M.	S. D. ±	Form II M.	S. D. ±	500 mg. Form I M.	S. D. ±	Form II M.	S. D. ±
0	0.87	0.11	0.89	0.06	1.05	0.28	0.85	0.23	0.81	0.20	0.83	0.09	0.87	0.06	1.09	0.39	1.09	0.33
2	0.90	0.16	0.91	0.07	1.04	0.24	0.85	0.14	0.94	0.10	1.02	0.08	0.89	0.05	1.20	0.35	1.15	0.31
4	1.20	0.20	1.11	0.24	1.18	0.25	1.19	0.15	1.05	0.12	1.39	0.21	1.21	0.10	1.66	0.46	1.61	0.23
6	1.22	0.14	1.12	0.10	1.24	0.31	1.29	0.16	1.09	0.12	1.33	0.16	1.23	0.21	1.74	0.51	1.78	0.51
24	1.14	0.06	0.95	0.19	1.21	0.30	1.13	0.27	0.97	0.20	1.13	0.13	0.99	0.16	1.49	0.35	1.49	0.55
48	0.95[b]	—	0.92[b]	—	1.08	0.35	1.20[d]	—	0.80[c]	—	0.98[c]	—	0.86[d]	—	1.26	0.51	1.31	0.49
72	0.93[c]	—	0.89[c]	—	1.03	0.14	1.27[e]	—	0.89[e]	—	0.98[e]	—	0.90[e]	—	1.16	0.41	1.23	0.43

[a] Based on readings for 5 subjects except where otherwise indicated. [b] Based on reading for 4 subjects. [c] Based on readings for 3 subjects. [d] Based on readings for 2 subjects. [e] Based on readings for 1 subject.

levels within each time period. Nevertheless, as an additional precaution, time of day was equalized on both sides of each pair compared in Table VI where time was not the variable under study.

PART II—SINGLE-DOSE STUDIES

The means and standard deviations for plasma tocopherol levels before and at different intervals after single oral administrations of *dl*-alpha-tocopherol acetate in form of the aqueous emulsions employed at dose levels of 100, 200, 400, and 500 mg. and in form of capsules (100 mg. doses) are recorded in Table III.

The mean differences and statistical significance of the mean differences between pairs of changes from control readings under corresponding conditions secured at various times after the administration of the various amounts and forms of vitamin E are tabulated in Table VI, Part I. The summary of the mean maximum rises in plasma tocopherol levels are recorded in Table VII.

When all single-dose paired increases were combined, increases with Form I were found significantly greater than those with Form II. The mean maximum rise in the plasma tocopherol level in all single-dose experiments was also greater for Form I than for Form II, with the exception of the single-dose experiment at the 500 mg. dose level (see Table VII). In this case II was productive of a greater rise than I, but the difference was too small to have any significance.

Single doses of 100 mg. of Form I or 200 mg. of Form II gave statistically significant increases above the morning control level with the pairing procedure even with the small samples available. Increase of the dose to 500 mg. was necessary with Form I before further significant increases were clearly demonstrated. With Form II even this increase gave borderline results. For both forms increase at 4 hours exceeded to a highly significant degree those at 2 hours, but increases between 4 and 6 hours were too small to be statistically significant for samples of this size. Increases with 100 mg. of Form I were significantly greater than those with 100 mg. of the capsules. One hundred mg. of Form II took an intermediate position, yielding a greater mean increase under corresponding conditions than the capsules, but a lesser mean increase than Form I.

The means and standard deviations for plasma tocopherol levels before and at different intervals after single intramuscular administrations of *dl*-alpha-tocopherol in sesame oil (100 and 500 mg. doses), of *dl*-alpha-tocopherol in an aqueous emulsion (100 mg. doses), and of *dl*-alpha-tocopherol monosodium phosphate in an aqueous solution (100 mg. doses) are recorded in Table IV. The intramuscular administration of a single dose of 100 mg. each of these three preparations and of 500 mg. of *dl*-alpha-tocopherol in sesame oil was not followed by a significant rise in the mean plasma tocopherol level at 2, 4, 6, or 24 hours. The summary of the mean maximum rises in plasma tocopherol levels is recorded in Table VII.

No analysis by means of pairs of observations for the same individuals was attempted since, with two exceptions, no single individual received more than one type of intramuscular injection. The analysis undertaken consisted simply of computing the significance of the difference between each of the group means and the means of the initial control readings.

PART III—LONG-TERM STUDIES

The means and standard deviations for plasma tocopherol levels before and at different intervals during a period of daily oral administration of *dl*-alpha-tocopherol acetate in form of the aqueous emulsions employed (100 and 500 mg. doses), in form of capsules (100, 400, and 500 mg. doses), and in form of tablets (400 mg. doses) are recorded in Table V. The mean maximum rises are given in Table VII. The mean maximum rise was greater for Form I than for Form II at the 100 mg. dose level, but at the 500 mg. dose level the mean maximum rises for both forms were approximately equal.

The long-term dosage experiments were also analyzed by the method of paired increase readings previously described for the single-dose studies, the only difference being that the

TABLE IV

The Means[a] and Standard Deviations for Plasma Tocopherol Levels (mg. per cent) Following the Intramuscular Injection of Various *dl*-alpha-tocopherol Preparations

	100 mg.						500 mg., sesame oil	
	Aqueous		Sesame oil		Monosodium phosphate			
Hours	Mean	S. D. ±	Mean	S. D. ±	Mean	S. D. ±	Mean	S. D. ±
0	0.92	0.29	0.94	0.09	1.03	0.15	0.90	0.09
2	0.92	0.24	0.94	0.12	0.85	0.16	0.88	0.10
4	0.94[b]	0.27	0.91	0.11	1.02	0.09	0.89	0.17
6	0.89	0.22	0.91	0.08	1.06	0.08	0.90	0.10
24	0.97	0.30	0.91	0.10	1.09	0.18	0.85	0.12
48	0.97	0.30	0.95	0.05	1.03	0.13	0.92	0.13
72	0.87	0.27	0.93	0.06	1.10	0.15	0.92	0.12

[a] Based on readings for 5 subjects except where otherwise indicated. [b] Based on readings for 4 subjects.

TABLE V

The Means[a] and Standard Deviations for Plasma Tocopherol Levels (mg. per cent) Following the Daily Oral Administration for 12 Days of Various *dl*-alpha-tocopherol Acetate Preparations

	100 mg.						400 mg.				500 mg.					
	Form I		Form II		Capsule		Capsule		Tablet		Form I		Form II		Capsule	
Days	M.	S. D. ±	M.	S. D. ±	M.	S. D. ±	M.	S. D. ±	M.	S. D. ±	M.	S. D. ±	M.	S. D. ±	M.	S. D. ±
1	1.18	0.17	1.06	0.33	1.06	0.31	1.19	0.09	1.06	0.31	0.99	0.14	0.97	0.18	1.27	0.11
2	1.48	0.18	1.35	0.37	1.14	0.35	1.66	0.17	1.72	0.40	1.49	0.43	1.55	0.32	1.87	0.52
3	1.52	0.20	1.35	0.46	1.33	0.38	1.87	0.33	1.56	0.32	1.48	0.48	1.58	0.50	1.77	0.34
4	1.58	0.13	1.28	0.43	1.30	0.40	1.91	0.16	1.72	0.45	1.49	0.48	1.58	0.58	1.63	0.23
5	1.43	0.11	1.18	0.33	1.33	0.44	1.66	0.17	1.64[b]	0.48	1.72	0.42	1.70	0.41	1.69	0.18
8	1.76	0.20	1.34	0.44	1.40	0.45	1.69	0.10	1.80	0.59	2.04	0.63	1.98	0.76	1.71	0.24
10	1.55	0.10	1.36	0.53	1.53	0.52	1.77	0.22	1.93	0.49	1.86	0.53	1.67	0.32	1.98	0.34
12	1.51	0.13	1.27	0.30	1.36	0.46	1.83	0.25	1.84	0.51	2.01	0.59	1.72	0.47	1.77	0.31

[a] Based on readings for 5 subjects except where otherwise indicated. [b] Based on readings for 4 subjects.

averages of the increases for the second, third, fourth, fifth, eighth, tenth, and twelfth days were paired instead of the individual increase readings (see Table VI, Part II). This variation in procedure was adopted since the increase readings for consecutive days for the same individual did not fully meet the requirements of independence of observations.* Since the samples were excessively reduced by the use of averages, findings on this basis were not statistically significant at the 1 per cent level of significance in any comparison and fell below the 5 per cent level in only three comparisons, namely, 500 with 100 mg. of Form II and 500 and 400 with 100 mg. of the capsules. Nevertheless, the means of the paired mean differences again indicated that the greatest increases were secured with Form I. Increases with Form II, the capsules, and the tablets showed little difference. With an increase in the size of the samples, higher levels of significance would undoubtedly have been obtained.

The long-term dosage experimental data were also analyzed as if the daily paired readings met the random sampling requirement of independence, that is, as if the readings for each day were for a different and randomly selected normal individual and were therefore independent of the readings for the preceding and following days. The statistical findings by this method are tabulated in footnotes *b–o* in Table VI, Part II. This procedure increased the significance level of mean differences and gave high significance findings in three dosage comparisons.

To ascertain further whether the prolonged administration of *dl*-alpha-tocopherol prep-

*Tests for intraclass correlation among repeated paired increase readings for the same individual in the long-term dose studies gave findings of significance in one test, borderline significance in a second, and nonsignificance in a third (by definitions in footnote *c* in Table VI).

TABLE VI

Effect of Vitamin E Preparations on Blood Levels of Vitamin E: Mean Differences and Statistical Significance of Mean Differences between Pairs of Changes from Control Readings under Corresponding Conditions Secured at Various Times after Administration of Various Amounts and Forms of Vitamin E

PART I. SINGLE DOSE STUDIES

Items paired[a]			Number of available pairs	Mean difference between paired increase readings	Standard error of mean difference	t	Probability (P) of occurrence of mean difference if true difference is zero[b]	Interpretation of statistical significance[c]
				mg. per cent				
A. General comparisons								
1. All doses, Forms I and II	Minus	No drug	111	+0.320	0.026	12.48	Less than 0.001	Highly significant
2. All doses, Form I	Minus	All doses, Form II	45	+0.088	0.032	2.75	0.001–0.01	Significant
B. Dosage comparisons (in mg.)								
1. Form I								
a. 100 I	Minus	No drug	15	+0.249	0.055	4.53	Less than 0.001	Highly significant
b. 200 I	Minus	100 I	9	+0.076	0.040	1.89	0.05 –0.1	Not significant
c. 400 I	Minus	100 I	9	+0.041	0.039	1.04	0.3 –0.4	Not significant
d. 500 I	Minus	100 I	6	+0.188	0.062	3.02	0.02 –0.05	Borderline
e. 400 I	Minus	200 I	9	+0.054	0.052	1.06	0.3 –0.4	Not significant
f. 500 I	Minus	200 I	12	+0.208	0.064	3.26	0.001–0.01	Significant
g. 500 I	Minus	400 I	6	+0.020	0.080	0.25	0.8 –0.9	Not significant
2. Form II								
a. 100 II	Minus	No drug	15	+0.175	0.060	2.93	0.01 –0.02	Borderline
b. 200 II	Minus	No drug	12	+0.232	0.061	3.77	0.001–0.01	Significant
c. 200 II	Minus	100 II	9	+0.054	0.061	0.89	0.3 –0.4	Not significant
d. 400 II	Minus	100 II	6	+0.042	0.052	0.80	0.4 –0.5	Not significant
e. 500 II	Minus	100 II	6	+0.345	0.112	3.07	0.02 –0.05	Borderline
f. 400 II	Minus	200 II	9	−0.010	0.070	0.14	0.8 –0.9	Not significant
g. 500 II	Minus	200 II	9	+0.226	0.115	1.97	0.05 –0.1	Not significant
h. 500 II	Minus	400 II	9	+0.236	0.078	3.01	0.01 –0.02	Borderline
C. Comparisons by time after drug administration								
1. Form I								
a. 4 hrs.	Minus	2 hrs.	20	+0.370	0.034	10.84	Less than 0.001	Highly significant
b. 6 hrs.	Minus	4 hrs.	20	+0.033	0.031	1.05	0.3 –0.4	Not significant
2. Form II								
a. 4 hrs.	Minus	2 hrs.	20	+0.273	0.048	5.68	Less than 0.001	Highly significant
b. 6 hrs.	Minus	4 hrs.	20	+0.059	0.056	1.04	0.3 –0.4	Not significant
D. Comparisons of capsules with Forms I and II by dosage (in mg.)								
1. 100 Form I	Minus	100 capsules	9	+0.166	0.047	3.55	0.001–0.01	Significant
2. 100 Form II	Minus	100 capsules	9	+0.068	0.029	2.32	0.02 –0.05	Borderline

[a] Comparisons were always made between two increase readings for the same person. Before pairing, individual readings were converted to mg. per cent change from control readings for the same person under corresponding conditions. The increase readings paired were always taken under conditions that corresponded in all specifications except that involved in the comparison (namely, difference in drugs, in dosage of the same drug, or in time elapsed after administration). A plus sign (+) on the mean difference indicates that the first type of increase listed (from which the second type was always *subtracted*) was on the average higher than the second, and a minus sign (−) indicates the reverse.

[b] Probabilities are evaluated in terms of both tails of the distribution. To secure chances in 100 that the difference is due to chance, multiply P by 100.

[c] If the chances of a difference of this amount in either direction are less than 5 in 100, but greater than 1 in 100, the significance is termed borderline; if less than 1 in 100 but greater than 1 in 1000, it is termed significant; if less than 1 in 1000, it is termed highly significant.

arations significantly increased the plasma levels of free tocopherol beyond those characteristic of single-dose results, a straight line was fitted to each set of long-term data and its slope (b) ascertained. The greatest daily increase was found to occur with 500 mg. of Form I. In this instance the average daily increase above the level of the preceding day occurring between the first and twelfth day amounted to +0.059 mg. and was statistically significant.* The average daily increase with

* The 35 individual increases over the control day were used in the computation of each *b*, since the use of means for individuals would have entirely eliminated the slope, the characteristic under study. Since the 7 readings for each individual were not fully independent, the degrees of freedom and hence the significance are overstated.

TABLE VI (*Cont.*)

Effect of Vitamin E Preparations on Blood Levels of Vitamin E: Mean Differences and Statistical Significance of Mean Differences between Pairs of Changes from Control Readings under Corresponding Conditions Secured at Various Times after Administration of Various Amounts and Forms of Vitamin E

PART II. LONG-TERM STUDIES

Items paired[a]			Number of individuals paired long term means were available[b]	Mean difference between paired means	Standard error of mean difference[b]	t[b]	Probability (P) of occurence of Mean difference if true difference is zero[b, c]	Interpretation of statistical significance[b*,d]
				mg. per cent				
A. Dosage comparisons (in mg.)								
1. Forms I and II								
a. 500 Form I	Minus	100 Form I	2	+0.716	0.306	2.34	0.2 –0.3	Not significant[e]
b. 500 Form II	Minus	100 Form II	4	+0.444	0.108	4.10	0.02 –0.05	Borderline[f]
2. Capsules								
a. 500 capsules	Minus	100 capsules	2	+0.167	0.010	16.72	0.02 –0.05	Borderline[g]
b. 400 capsules	Minus	100 capsules	4	+0.276	0.058	4.75	0.01 –0.02	Borderline[h]
B. Drug Comparisons at Same Dosage Levels								
1. 500 Form I	Minus	500 Form II	3	+0.115	0.121	0.95	0.4 –0.5	Not significant[i]
2. 100 Form I	Minus	100 Form II	5	+0.124	0.053	2.35	0.05 –0.1	Not significant[j]
3. 100 Form I	Minus	100 capsules	5	+0.085	0.076	1.12	0.3 –0.4	Not significant[k]
4. 100 Form II	Minus	100 capsules	5	−0.039	0.033	1.18	0.3 –0.4	Not significant[l]
5. 500 Form II	Minus	500 capsules[m]	2	+0.026	0.032	0.82	0.5 –0.6	Not significant[n]
6. 400 capsules	Minus	400 tablets	2	−0.134	0.290	0.46	0.7 –0.8	Not significant[o]

[a] Comparisons were always made between two mean increase readings for the same person, each mean being based on 7 readings, one each for the 2nd, 3rd, 4th, 5th, 8th, 10th, and 12th days after the beginning of the administration of the drug daily in the dosage indicated. For further specifications regarding pairing, see sentence 2 and following of footnote *a*, Part I of this table.

[b] The long-term dosage experimental data were also analyzed *as if* the daily paired readings met the random sampling requirement of independence, that is, *as if* the readings for each day were for a different and randomly selected normal individual and were therefore independent of the readings for the preceding and following days. (The readings for the same day were still assumed to be for the same individuals and therefore suitable for the pairing of dosage results, etc.) This procedure had the effect of multiplying the number of available pairs by 7 and thus greatly increasing the number of degrees of freedom while at the same time retaining the same mean differences. In consequence, the standard errors of the mean differences were usually greatly reduced and the chances of a "significant" verdict, greatly increased. The results on this basis are reported in footnotes *e* through *l* and footnotes *n* and *o*. Since an application of the technique of analysis of variance indicated that some intraclass correlation did exist among repeated observations for the same individuals on these long-term studies and that therefore the requirement of independence assumed in this latter procedure actually was not met, preference is given in the tabular presentation to the more conservative procedure of pairing only the *means* for individuals for the entire period of observation with a given drug and dosage (7 readings per mean).

[c] See footnote *b*, Part I of this table.

[d] See footnote *c*, Part I of this table.

[e] By the method of footnote *b*, t becomes 5.81, P < 0.001 and the interpretation becomes "highly significant."

[f] By the method of footnote *b*, t becomes 7.17, P < 0.001 and the interpretation becomes "highly significant."

[g] By the method of footnote *b*, t becomes 2.73, P = 0.01–0.02 and the interpretation remains "borderline."

[h] By the method of footnote *b*, t becomes 5.83, P < 0.001 and the interpretation becomes "highly significant."

[i] By the method of footnote *b*, t becomes 1.61, P = 0.1–0.2 and the interpretation remains "not significant."

[j] By the method of footnote *b*, t becomes 3.58, P = 0.001–0.01 and the interpretation becomes "significant."

[k] By the method of footnote *b*, t becomes 1.97, P = 0.05–0.1 and the interpretation remains "not significant."

[l] By the method of footnote *b*, t becomes 1.16, P = 0.2–0.3 and the interpretation remains "not significant."

[m] No comparison is made of 500 mg. Form I with 500 mg. capsules since only 1 set of pairs was available.

[n] By the method of footnote *b*, t becomes 0.65, P = 0.5–0.6 and the interpretation remains "not significant."

[o] By the method of footnote *b*, t becomes 1.32, P = 0.2–0.3 and the interpretation remains "not significant."

100 mg. of the capsules amounted to +0.022 mg. and was of borderline significance. All other increases were of lesser amounts and were not statistically significant for samples of this size.* The daily averages followed no consistent pattern (see Table V), but in most series the maximum mean level was reached between the eighth and tenth day. It must be emphasized that the available data relate to only five individuals who may, or may not, be representative of the general effect on normal persons of a 12-day period of administration. The findings as to slope may also not be presumed to extend beyond the twelfth day, the last day tested.

*The remaining slopes (b's) were as follows: 500 mg. Form II, +0.021; 100 mg. Form I, +0.007; 100 mg. Form II, −0.0004; 500 mg. capsules, +0.007.

Discussion

The mean maximum rise in the plasma tocopherol level was markedly greater for Form

TABLE VII

Summary of the Mean Maximum Rises in Plasma Tocopherol Levels (mg. per cent) for the Oral and Parenteral Administration of Various Vitamin E Preparations

Single dose experiments (oral administration)			
	dl-alpha-tocopherol acetate		
Amount administered	Aqueous dispersion, Form I	Aqueous dispersion, Form II	Capsules
mg.			
100	0.42	0.30	0.20
200	0.48	0.32	—
400	0.57	0.43	—
500	0.65	0.73	—

Single dose experiments (intramuscular administration)			
	dl-alpha-tocopherol		
Amount administered	In oil	In aqueous dispersion	Phosphate
mg.			
100	0.05	0.11	0.09
500	0.08	—	—

Multiple dose experiments (oral administration)				
	dl-alpha-tocopherol acetate			
Amount administered	Form I	Form II	Capsules	Tablets
mg.				
100	0.60	0.41	0.51	—
400	—	—	0.81	0.88
500	1.12	1.09	0.85	—

I than for Form II after single doses of 100 200, and 400 mg. and after repeated doses of 100 mg., as was also the mean rise for all the single-dose data combined, as analyzed in the paired increase analysis. However, when 500 mg. were given, the respective mean maximum rises attained with either preparation, in the single-dose and the multiple-dose experiment, were about equal. This would indicate that at this high dose level, the maximum results obtainable with either a single dose or with repeated doses are obtained also with the less active II preparation.

It is also clear from the data for Forms I and II recorded in Table VII that the mean maximum rises in vitamin E plasma levels following single doses increased only moderately with increases in dosage. Repeated doses at the 100 mg. level also produced levels of the same order of magnitude as single doses of 400 mg. Daily 500 mg. doses were, however, productive of a substantially greater increase. The analysis by means of paired increase readings also suggests the increased effectiveness of 500 mg. of either form of tocopherol as compared with 100 mg.

In the single-dose experiment with 100 mg. of *dl*-alpha-tocopherol acetate in form of capsules, both the mean rise (paired readings analysis) and the mean maximum rise in the plasma tocopherol level were smaller than in the corresponding experiments with Forms I and II. However, in the multiple-dose experiments Ephynal acetate capsules (100 mg./day) yielded better mean increases and mean maximum increases than Form II, but not as large increases as Form I. If this is not a chance fluctuation, perhaps the somewhat poorer absorption of the Ephynal acetate capsule is offset to a certain degree by continued administration. However, with 500 mg./day of the Ephynal acetate capsules the results were again not as good as with either Forms I or II.

As for the single-dose experiments by the parenteral route, it appears that the rises in plasma tocopherol levels are insignificant. Even a 500 mg. dose of *dl*-alpha-tocopherol in oil raised the vitamin E level at the maximum point only by a mean of 0.08 mg. per cent. Apparently, tocopherol is not absorbed from the oily vehicle. Similarly, there is no significant absorption from the aqueous emulsion of tocopherol at the 100 mg. level. Since also the monosodium phosphate of tocopherol is not productive of any noteworthy increase in the tocopherol level, this salt is either not hydrolyzed, or, if it is, the tocopherol is not absorbed from the tissues. Possibly the absorption is extremely slow and therefore not detected by the method used.

The parenteral administration of vitamin E is ineffectual, regardless of the type of compound (free alcohol or monosodium phosphate) and the type of vehicle (oil or water) used. Only oral administration markedly raises the plasma tocopherol level. Best results by the latter route are obtained if high single doses (500 mg.) are given daily for a period of time.

The increases of plasma tocopherol levels found in these studies are lower than those reported by Klatskin and Krehl.[1] However, all of the subjects included in their study were hospitalized patients. They have reported a mean maximum rise of 1.31 mg. per cent after the oral administration of 500 mg. of *dl*-alpha-tocopherol acetate as compared to a maximum rise of 0.73 mg. per cent recorded in this study. Similarly, following a single intramuscular injection of 500 mg. of *dl*-alpha-tocopherol in oil, Klatskin and Krehl found an increase of plasma tocopherol level of 0.60 mg. per cent as compared to an increase of 0.08 mg. per cent reported in this study. Yet their findings and ours suggest that the rise in plasma tocopherol level after intramuscular injection of *dl*-alpha-tocopherol is significantly smaller than that following the oral administration of *dl*-alpha-tocopherol acetate.

Conclusions

The amount, route of administration, and vehicle used are important in determining the effectiveness of vitamin E preparations in increasing the plasma level of free tocopherol.

Single oral doses of 200, 400, 500 mg. and sometimes of 100 mg. of *dl*-alpha-tocopherol acetate are effective in increasing the free tocopherol plasma level to a significant degree after six hours.

Repeated daily oral doses produce somewhat greater maximum increases than single oral doses.

The parenteral administration of vitamin E is ineffectual in increasing the free tocopherol plasma level, regardless of the type of compound (free alcohol or monosodium phosphate) and the type of vehicle (oil or water) used.

These results are not to be interpreted as implying any conclusions as to the therapeutic effectiveness of vitamin E.

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Resumen

Efectos de los preparados vitamínicos E sobre los niveles plasmáticos de tocoferol

La cantidad, método de administración, y vehículo empleado son importantes en determinar la eficacia de los preparados de vitamina E para aumentar el nivel plasmático de tocoferol libre.

Dosis orales de 200, 400, 500 mg., y a veces de 100 mg. de acetato de *dl*-tocoferol, son efectivas en aumentar el nivel de tocoferol libre en el plasma a un grado significativo después de seis horas.

Dosis orales repetidas cada día producen aumentos máximos mayores que los conseguidos por dosis orales únicas.

La administración parentérica de vitamina E no es efectiva en aumentar el nivel plasmático de tocoferol libre, cualquiera sea el tipo de compuesto (alcohol libre o fosfato de monosodio) o el tipo de vehículo (aceite o agua) empleado.

Estos resultados no han de interpretarse como implicando cualquier conclusión respecto a la eficacia terapéutica de la vitamina E.

The Effect of VITAMIN SUPPLEMENTATION *on* SOLDIERS *Residing in a* COLD ENVIRONMENT

PART II. PSYCHOLOGICAL, BIOCHEMICAL, AND OTHER MEASUREMENTS

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INTRODUCTION

PART I of this paper,[19] which appeared in the previous issue of this JOURNAL, described the organization and conduct of the test and gave the results of the studies on physical performance and cold exposure. This paper presents the results of the studies on psychological and biochemical measurements. The tables, figures, and bibliographic references are numbered serially with those of Part I.

METHODS AND RESULTS

PSYCHOLOGICAL TESTS

A battery of six psychological tests were administered to all the test subjects at intervals during the experiment. The tests used were as follows:

1. Pole Mountain Attitude Questionnaire. This test consisted of a series of six questions which were formulated specifically for this experiment and were designed to give information about the attitude of the test subjects toward the experiment. The answers to the questions were scored as favorable, unfavorable, or neutral (did not answer).

2. Minnesota Multiphasic Personality Inventory. This is a standard psychological test published by The Psychological Corporation of New York City. The subjects answered the questions on standard IBM answer forms and the tests were machine graded by the Institute for Psychological Services of the Illinois Institute of Technology. Each of the standard scores was recorded.

3. Army Attitude Survey. This test, consisting of 50 questions, was adapted from an Air Force Attitude Survey supplied to us by Dr. Saul Sells of the Department of Clinical Psychology, School of Aviation Medicine, Randolph AFB, Texas. The answers were scored as favorable or unfavorable from a key provided by Dr. Sells. This key utilized only 16 of the 50 questions. An additional 10 questions were keyed for scoring by us and each test was scored by both keys.

4. Sociometric Rating. In this test the men rated their squad mates in the categories of Officer Aptitude and Adjustment. Each man assigned a rank number to himself and to

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The opinions expressed in this paper are those of the authors and do not necessarily represent the official views of any governmental agency.

each of his squad mates for these categories. The mean rank scores were converted to percentage of range in order to adjust for differences in size of squads.

5. Digit Symbol Substitution Test. This is one of the subtests in the Wechsler-Bellevue Intelligence Scale which is published by The Psychological Corporation. A fixed time (1 minute) is allowed for performance of the test and the score is computed by subtracting number of wrong answers from number of right answers.

6. Multiple Addition Test. Although there are no standardized forms for this test, it is a frequently used tool in psychological laboratories. The score was computed by subtracting the number of wrong answers from the number of right answers accomplished in a fixed time (2 minutes).

Schedule of Testing

All tests were administered twice to each subject, once during the second week and once during the tenth week of the experiment. In addition, the Minnesota Multiphasic Personality Inventory and Sociometric Rating tests were given during the fifth week.

Results

In all instances the results of the psychological tests were analyzed for differences in scores between the first and last administration.

Pole Mountain Attitude Questionnaire. A tabulation was made of each subject's answer to each question for both administrations. A score was then assigned on the basis of the subject's change in answer according to the following scheme:

1st Administration	2nd Administration	Score
F	F	0
F	N	−1
F	U	−2
N	F	+1
N	N	0
N	U	−1
U	F	+2
U	N	+1
U	U	0

F denotes a favorable answer, U unfavorable, and N neutral. The mean scores for the control and supplemented groups were obtained and differences between these means were tested for statistical significance. No significant differences were discernible between the two treatment groups either in regard to comparisons at each administration period or in regard to scores for changes in answers between administrations. For the test group as a whole there were no great changes in attitude as measured by this test between the first and second administration.

Minnesota Multiphasic Personality Inventory. Each of the standard scores was listed for each man for each administration. Each subject's score for each personality factor on the first test was subtracted from his score on the third test. From these differences the mean differences for the control and supplemented groups were calculated. The differences between these mean differences were then analyzed for statistical significance using the "*t*" test. No statistically significant differences between the control and supplemented groups occurred.

Attitude Survey. As indicated above, this test was scored by two different keys, one allowing a maximum score of 16, the other a maximum score of 26. An exact analysis of covariance was carried out on each scoring system using the final score as the variate and the initial score as the covariate. The *F* values for treatment difference were 0.098 and 0.121, respectively. Neither value approaches levels of significance.

Sociometric Rating. Raw scores for ranks were converted to per cent of range by the following formula:

$$\% \text{ of range} = \frac{\text{Sum of Ranks}}{(\text{Range})^2} \times 100$$

where sum of ranks is the sum of the individual ranks assigned to each man by his squad mates and range is total number of men in the squad. An exact analysis of covariance was carried out for each of the two categories, officer aptitude and adjustment, using score in the final test as the variate and score in the initial test as the covariate. The *F* values were 0.178 and

TABLE XXIII

Mean Systolic and Diastolic Blood Pressure in Supplemented and Control Groups by Platoons in the First, Second, Fifth, and Ninth Weeks

Platoon	First week		Second week		Fifth week		Ninth week	
	Control	Supplemented	Control	Supplemented	Control	Supplemented	Control	Supplemented
I	144/77	122/77	121/80	119/77	122/78	120/77	124/62	118/62
II	116/80	114/74	120/78	119/78	120/76	121/80	118/62	120/65
III	109/75	123/88	120/78	120/81	118/74	119/77	117/62	116/62
IV	116/83	120/84	121/80	122/81	119/77	121/79	120/64	122/66
Company	114/79	120/81	120/79	120/79	119/76	120/78	120/62	119/63

0.244, respectively, indicating that there was no significant difference between the treatment groups in regard to changes in Sociometric Rating scores in the course of the experiment.

Digit Symbol. An exact analysis of covariance using the score of the last test as the variate and that of the first test as covariate gave an F value of 0.835 for treatment differences, a nonsignificant value.

Multiple Addition. An exact analysis of covariance using the score of the last test as the variate and that of the first as the covariate gave an F value for treatment differences of 0.135, a nonsignificant value.

PHYSICAL EXAMINATION

Physical examination and brief medical history were performed during the first week of the test period. No significant abnormal physical findings were revealed.

Examination for the signs of vitamin deficiency and nutritional status were made during the second, fifth, and ninth weeks. Criteria for the determination of stigmata and the examination technique were established. Examinations were performed in natural daylight by the same observer on all occasions. The presence of any positive physical findings was checked by another observer to minimize the subjective element of the examination.

Results

No physical findings justifying the diagnosis of any vitamin deficiency or of nutritional disturbance due to caloric deprivation were encountered. Borderline changes observed in the eyes, lips, and nose were probably attributable to exposure to the elements. The patellar and Achilles hyporeflexia encountered may well be attributed to the effects of the walking exercise which formed a large portion of the energy expenditure, particularly in the last phase of the study.

Blood Pressure

Blood pressure was measured in the sitting position, recording the systolic and diastolic pressures at the point where the sound appeared or disappeared, respectively. Determinations were made during the first, second, fifth, and ninth weeks. The results are presented in Table XXIII. There were no marked differences between the groups. Blood pressures taken after three weeks of reduced caloric intake showed a uniform decrease in the diastolic pressure.

A lowering of blood pressure is to be expected during periods of uncomplicated severe malnutrition. This is usually accompanied by a lowering of the pulse pressure.[20] The decrease in diastolic pressure with unchanged systolic pressure encountered in this study with only a moderate weight loss is of unknown significance.

ANTHROPOMETRICS AND BODY WEIGHTS

Anthropometric measurements were made four times on each man during the course of the experiment. Body weights were taken at weekly intervals. These measurements were made for two purposes: (1) to define the composition of the test group for comparison with other populations, and (2) to compare the two randomly chosen subgroups, as to initial similarity and as to progressive changes occurring through the course of the experiment.

TABLE XXIV

Summary of Body Weights*

Phase of study →	Control	Equilibration			4000 cal.			R & R	2500 cal.		2000 cal.	
Serial weighing number →	1	2	3	4	5	6	7	8	9	10	11	12
Days after capsules started →	−3	0	+5	+12	+19	+28	+33	+40	+47	+51	+54	+61
Control												
Mean	70.40	70.65	70.68	70.27	70.29	69.90	70.07	70.22	68.60	68.37	67.34	66.31
S. D.	11.53	11.17	11.24	11.35	10.99	10.71	10.79	10.18	9.82	9.77	9.53	9.07
Supplemented:												
Mean	72.16	72.64	72.29	71.97	71.60	70.86	71.04	71.04	69.24	68.90	68.05	67.05
S. D.	9.35	8.93	8.62	8.43	8.18	8.20	8.09	7.73	7.58	7.60	7.46	7.36

* Missing data were interpolated proportionately to adjacent values so that all values of the table are based on 42 control and 44 supplemented subjects.

TABLE XXV

Summary of Analyses of Covariance

Analysis no.	Name of test	Variate	Covariate	Unadjusted means: Control N	Control Variate	Control Covariate	Supplemented N	Supplemented Variate	Supplemented Covariate
1	Body weight	10th wk.	0 wk.	42	66.31	70.40	42	66.69	71.89
2	Body weight	7th wk.	0 wk.	42	70.22	70.40	43	70.87	72.04
3	% body fat	10th wk.	1st wk.	42	3.47	6.93	44	3.35	7.76
4	Eosinophils	% of Control, FM	% of control, basal	42	36.14	112.17	44	30.71	94.95
5	Eosinophils	% of Control, FM	1st count	39	35.93	198.38	41	31.50	166.61

Analysis no.	Means of variates Adjusted for covariance: Control	Suppl.	Difference between adjusted means, control minus supplemented: Diff., a	Standard error	F ratio	P	95% confidence limits: L_1	L_2	Coefficient of regression of variate on covariate: Regression coefficient γ	Standard error	t	P
1	66.88	66.12	0.77	0.35	4.741	0.04	+1.46	+0.07	0.7717	0.0178	43.403	0.001
2	70.91	70.19	0.71	0.42	2.953	0.08	+1.54	+0.11	0.8421	0.0213	39.517	0.001
3	3.64	3.18	0.47	0.22	4.732	0.04	+0.90	+0.04	0.3975	0.0262	15.166	0.001
4	36.45	30.27	6.18	2.38	6.721	0.02	+10.92	1.44	−0.0315	0.0277	1.135	0.25
5	36.06	31.26	4.79	2.41	3.968	0.05	+9.58	0.00	0.0095	0.0152	0.624	0.55

Age

Age in whole years to the nearest birthday was recorded at the onset of capsule administration. The majority of men were grouped between 18 and 27 years with a peak at 23 years, but 10 of the 86 men were older than 30 years, the eldest being 38. The arithmetic mean age of the control was 24.17 years; of the supplemented group, 24.41 years (Table XXVI). The difference between these means is not statistically significant.

Height

Height was measured to the nearest half-centimeter during each of the anthropometric examinations. The range of heights was 153 to 188.5 cm. and the median, 172 cm. The distribution was roughly normal and approximately the same for the two groups. Mean height and standard deviation of the control group was 174.62 ± 6.68 cm.; and of the supplemented group, 173.44 ± 6.70 cm. (Table XXVI). The difference between these means is not statistically significant. Height did not change perceptibly during the course of the experiment.

Weight

Men were weighed in the morning after arising and voiding and before breakfast. The range of weights was 52.3 to 97.4 Kg. with a median of about 71 Kg. The distribution is roughly of the normal type. Mean and standard deviation of the weights in the control group were 70.7 ± 11.2 Kg; and in the supplemented group, 72.7 ± 8.9 Kg. The difference between these means is not statistically significant.

Serial mean body weights of the control and supplemented groups are shown in Figure 9 and Table XXIV. Both groups tended to lose weight during the equilibration and high caloric intake, high energy output periods. The supplemented group lost at a more rapid rate, so that at the end of this period the difference of the mean weights was approximately one kilogram rather than two. Mean weight increased slightly during the week of rest and rehabilitation, then fell rapidly during the periods of caloric restriction. From

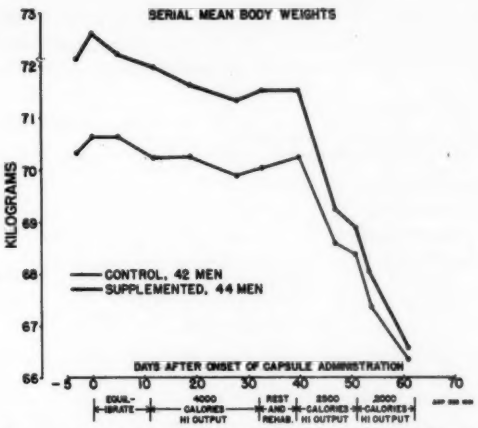

Fig. 9. Serial Mean Body Weight of Test Subjects During the Course of the Experiment.

the first to the last weighing periods the mean weight of the control group dropped 4.1 Kg. and of the supplemented group, 5.1 Kg. The mean loss for both groups was 3.9 Kg. during the three weeks of caloric restrictions or 1.2 Kg./week.

An analysis of covariance was carried out using the final body weight as the variate and the initial body weight as the covariate (See Table XXV, Analysis 1). The differences (control minus supplemented) between the means of the two treatment groups adjusted for covariance was 0.77 Kg. with the control group having the higher value. (It should be noted that at the beginning of the experiment the supplemented group had the higher mean body weight.) The 95 per cent confidence limits of this difference are 1.46 and 0.07 Kg. The F ratio of the difference was 4.741, giving a P value of 0.04, signifying statistical significance at the 4 per cent level of probability.

Another analysis of covariance was performed using the body weight at the seventh week (end of high calorie period) as the variate and the initial body weight as the covariate (Table XXV, Analysis 2). The difference between adjusted means was 0.71 Kg. with the control group having the higher value. (It should be noted that before adjustment for initial body weight the seventh week mean value of the supplemented group was higher than that of the control.) The 95 per cent confidence limits of this difference are 1.54 and 0.11 Kg. The F ratio was 2.953, giving a P value of 0.08, which is not statistically significant.

It was apparent that the men with the highest initial body weight sustained the largest losses in weight during the course of the experiment. Even when loss of weight was expressed as a percentage of initial weight, the men with the higher initial

TABLE XXVI

Summary of Anthropometric Data

Phase of study →	Equilibration		End high intake-high output*	End low intake-high output
Serial anthropometric number →	1	2	3	4
Days after capsules started →	+2	+9	+37	+61
Age (years):				
Control	24.17	—	—	—
Supplemented	24.41	—	—	—
Height (cm.)				
Control	174.62	—	—	—
Supplemented	173.44	—	—	—
"Per cent Body Fat" by skinfolds				
Control	6.93	5.68	5.00	3.47
Supplemented	7.76	5.95	5.14	3.35
Abdominal skinfold (mm.)				
Control	11.6	10.2	8.8	5.9
Supplemented	12.6	10.7	8.8	5.6
Chest skinfold (mm.)				
Control	7.9	6.5	5.8	4.0
Supplemented	9.3	6.9	6.1	3.7
Arm skinfold (mm.)				
Control	8.8	7.4	6.7	5.6
Supplemented	9.2	7.4	6.8	5.5
Back skinfold (mm.)				
Control	12.6	11.6	11.4	8.6
Supplemented	13.8	12.7	11.6	8.7

* One of the control subjects missed this examination. In all other cases 42 control and 44 supplemented subjects were measured.

weights showed the greater losses. This relationship is depicted graphically in Figure 10 where the regression of per cent change in body weight from week 0 to week 10 on initial body weight is computed. The mean per cent loss in body weight was 5.4 for the control group and 6.9 for the supplemented group. The b values or regression coefficients and their respective standard errors were 0.2020 ± 0.034 for the control group and 0.2318 ± 0.0568 for the supplemented group. The b values divided by their respective standard errors gave t values of 5.87 for the control group and 4.08 for the supplemented group, indicating that both of these regressions are statistically significant. The difference between the two b values was 0.0298 and its standard error was 0.0647, giving a t value of 0.46, indicating that the difference between the two b values is not statistically significant. The fact that these two regression coefficients do not differ significantly increases the validity of the observed statistically significant difference in weight loss between the control and supplemented groups.

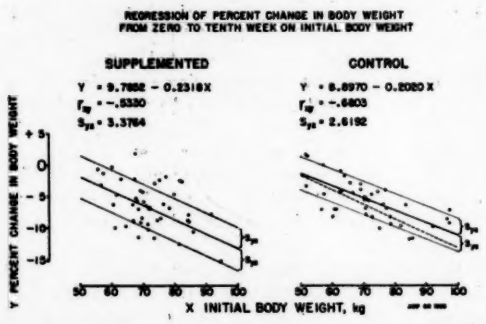

Fig. 10. Regression of Percent Change in Body Weight on Initial Body Weight.

"Per Cent Body Fat"

Brožek and Keys[21] have correlated multiple skinfold measurements with specific gravity in a large group of young men. They proposed a regression formula in which the specific gravity may be predicted from three selected skinfold measurements. Rathbun and Pace[22] set forth a tentative formula for the conversion of specific gravity to per cent body fat. It has been our experience that due to minor individualities of technique, different investigators using the same instrument on the same subject sometimes obtain different readings. To minimize this effect one medical officer did

all of the skinfold measurements of this study. However, the values calculated for "per cent body fat" from the above mentioned formulae were consistently lower than published norms for this age group (mean per cent fat of 133 college men was 10.9).[21] This difference is apparently due to differences in technique between the originators of the regression formula and the present investigator. It is our impression that relative values within a group, and serial values of a group each time measured by the same investigator may be compared with profit, but that the absolute values derived do not necessarily represent the true percentage of fat in the body; hence the quotation marks. It has been shown by Newman[23] that the state of body hydration and peripheral vascular filling may affect the thickness of the skinfolds, a further reason for accepting calculated values for "per cent body fat" with reservation.

In the present study, all measurements were made in the afternoon after lunch. Activity of the subjects before lunch was variable. Skinfold calipers were of the Medical Nutrition Laboratory design.[24] A transverse skinfold was measured to the right of the navel and one-third of the distance from the navel to the right mid-lateral line; a transverse skinfold was measured half-way between the right nipple and the apex of the right anterior axillary line; and a longitudinal skinfold was measured midway between the elbow and shoulder on the extensor surface of the right brachium.

The lowest calculated "per cent body fat" was 1.8 per cent; the highest, 17.0 per cent; and the median approximately 6.5 per cent. The distribution in the two treatment groups was reasonably similar. The arithmetic mean of the control group was 6.9 per cent and of the supplemented group, 7.8 per cent. This difference is not statistically significant.

The serial trend of these determinations is illustrated in Table XXVI. There was a remarkable drop in average values for "per cent body fat" occurring during seven days of the equilibration period. Body weight changes were not nearly great enough to explain these short-term differences. It is probable that the observed changes were due to differences in hydration and cutaneous capillary filling, as pointed out by Newman.[23]

A progressive decrease in the calculated "per cent body fat" was seen, and most probably was related to actual losses of body fat due to the high energy output with restricted caloric intake. It is noted that there is an actual crossing-over of mean values of the control and supplemented groups, suggesting that the supplemented group had a greater tendency to lose fat.

An analysis of covariance was carried out using the calculated per cent body fat at the tenth week as the variate and that at the first week as the covariate (Table XXV, Analysis 3). The difference (control minus supplemented) between the means of the two treatment groups adjusted for covariance was 0.47 per cent, with the control group having the higher mean per cent body fat. (It should be noted that at the beginning of the experiment the supplemented group had the higher mean value for per cent body fat.) The 95 per cent confidence limits of this difference are 0.90 and 0.04. The F ratio for this difference was 4.732, giving a P value of 0.04, indicating statistical significance at the 4 per cent level of probability.

Skinfold measurements from the three areas incorporated in the formula, as well as from the horizontal fold beneath the tip of the right scapula, showed an initial distribution of values similar to that of the calculated "per cent body fat" and showed roughly parallel degrees of progressively decreasing size. At all sites the mean skinfold thicknesses were initially greater for the supplemented than for the control group and became almost equal to or smaller than those of the control group at the time of the last examination.

MORBIDITY RECORDS

Sick Call Compilation

Table XXVII lists the number of men seen in the dispensary for illnesses and injuries. Only one entry is made for a single illness. The tabulation is divided by treatment groups and into three time periods: before treatment; 4000 calorie diet phase; 2500 calorie diet phase. Reactivation of previous leg injuries was not included.

Omitting pediculosis pubis and dental problems as having no conceivable relation to the

TABLE XXVII

Dispensary Visits for Various Causes Tabulated by Treatment Groups

	Weeks 0–1		Weeks 2–6		Weeks 7–9	
	Control	Supplemented	Control	Supplemented	Control	Supplemented
Illnesses						
Upper respiratory tract infections	16	10	16	10	5	0
Gastrointestinal disorders	1	0	4	1	10	5
Headache	1	0	3	1	1	2
Infections (other)	1	0	6	2	1	0
Pediculosis pubis	0	0	1	5	0	0
Dental	0	0	3	3	1	0
TOTALS	19	10	33	22	18	7
Trauma						
Feet (Orthopedic)	0	0	8	4	5	1
Blisters	0	0	5	7	7	1
Knees	0	0	4	3	1	1
Hands	0	1	1	3	1	0
Muscles	3	1	6	4	3	1
Other	2	0	1	0	1	3
TOTALS	5	2	25	21	18	7

treatment, and combining all entries during the treatment period, we arrive at the values presented in Table XXVIII.

TABLE XXVIII

Dispensary Visits for All Causes Except Dental Problems and Pediculosis Pubis

	Weeks 0–1		Weeks 2–9	
	Control	Supplemented	Control	Supplemented
Illness	19	10	46	21
Trauma	5	2	43	28
TOTAL	24	12	89	49

There is no indication of a significant effect of treatment in these data. From the data in Table XXVIII the incidence of illnesses in the control and supplemented groups in the period before and during capsule administration was analyzed in a fourfold table. The chi square was 0.004, a nonsignificant value. The control group showed a higher incidence of both illness and trauma both before and after beginning capsule administration.

BIOCHEMICAL MEASUREMENTS

Methods. The methods used for the biochemical determinations were as follows:

Determination	Authors of method	Bibliographic reference
Blood glucose	Nelson	25
Blood and urinary ascorbic acid	Roe and Kuether	26
Hemoglobin	Sanford and Sheard	27
Eosinophil count	Randolph	28
Urinary total nitrogen	Ma and Zuazaga	29
	Keys	30
Urinary creatinine	Peters	31
Urinary uric acid	Benedict and Franke	32
Urinary 17-ketosteroids	MRC Committee	33

All determinations were made by the original methods as described in the references listed above, except for urinary oxidized ascorbic acid. The determination of oxidized ascorbic acid in urine was accomplished by omitting treatment with activated charcoal and diluting the urine samples directly with 6 per cent trichloroacetic acid containing 0.1 per cent of freshly added thiourea. The diluted urine was then analyzed immediately by the Roe and Kuether[26] method. Total ascorbic acid in urine was determined by the unmodified method of Roe and Kuether using activated charcoal.

Collection of Blood Specimens. Blood was drawn by syringe from an antecubital vein, transferred to a test tube containing a few drops of a heparin solution, and mixed. All determinations on blood were made within a few hours after collection of the samples.

TABLE XXIX

Nitrogen Balance

Date	Control					Supplemented				
	Caloric intake	N intake	Urinary N excretion	Total N excretion	N balance	Caloric intake	N intake	Urinary N excretion	Total N excretion	N balance
	Cal./day		*Gm./day*			*Cal./day*		*Gm./day*		
18–19J	3566	18.7	12.2	13.7	+5.0	3429	17.6	12.1	13.6	+4.0
25–26J	3480	18.0	14.5	16.0	+2.0	3351	17.1	13.3	14.8	+2.3
17–18F	2500	12.1	12.5	14.0	−1.9	2488	12.0	12.6	14.1	−2.1
22–24F	2563	12.7	12.3	13.8	−1.1	2554	12.7	12.6	14.1	−1.4
26–27F	1980	10.8	11.5	13.0	−2.2	1989	10.9	11.5	13.0	−2.1
2–4M	1888	12.1	12.2	13.7	−1.6	2047	12.0	11.6	13.1	−1.1
5–6 M	1888	12.1	13.7	15.2	−3.1	2047	12.0	13.0	14.5	−2.5

Collection of Urine Specimens. Urine was collected in one-liter polyethylene bottles containing a few crystals of metaphosphoric acid as a preservative. The beginning and end of urine collection periods were accurately timed by having all men empty their bladders at the same time under supervision of the platoon lieutenants and platoon sergeants. Determinations of total and oxidized ascorbic acid were carried out immediately after collection of each set of urine samples. All other determinations on the urine samples were accomplished within 24 hours after collection except 17-ketosteroids, of which determinations were made on composite specimens shipped to the Chicago Laboratories of MNL.

Urinary Nitrogen Excretion

There was no significant difference in mean values for urinary total nitrogen in grams per day between the treatment groups. In Table XXIX are listed the estimated mean nitrogen balances at various times during the experiment. The nitrogen intake was calculated from the observed protein intake (see Table VI, Part I). The total nitrogen output was calculated by adding a constant factor of 1.5 Gm./day as an estimate of fecal nitrogen[34,35] to the observed urinary total nitrogen values. The nitrogen balance so calculated was moderately positive during the period when 4000 calories were offered in the diet and was slightly negative during the period when 2500 to 2000 calories were offered. No important differences in nitrogen balance between the two treatment groups were noted.

Urinary Ascorbic Acid Excretion

Table XXX gives the mean values for total urinary ascorbic acid expressed as mg. per day for the days on which 24-hour samples were run, together with the corresponding values for mean ascorbic acid intake. The latter values were calculated by adding the ascorbic acid content of the capsules (24 mg./day for the control group, 1200 mg./day for the supplemented group) to the values for ascorbic acid in the ingested food as derived from the food intake data (Table VII, Part I). It will be noted that the control group had a mean intake of 61 mg./day and excreted 12.6 mg./day, or 21 per cent of the intake, whereas the supplemented group with a mean intake of 1235 mg./day excreted 1024 mg./day, or 83 per cent of the intake. The difference between the oral intake and the urinary excretion was 48 mg./day for the control group and 211 mg./day for the supplemented group.

The data on total ascorbic acid in the fractional urine collections revealed no distinct trends in relation to diurnal variation or in relation to the type of activity for the day. Comparing the control days with the days of forced marches or cold exposure, there was no indication of an alteration of total ascorbic acid excretion as a result of these activities.

TABLE XXX

Ascorbic Acid Intake and Total Urinary Ascorbic Acid Excretion

Date	Control		Supplemented	
	Intake	Urinary excretion	Intake	Urinary excretion
	mg./day		*mg./day*	
19–20J	60	12.2	1234	988
26–27J	57	12.5	1231	1039
18–19F	65	13.0	1241	1044
Mean	61	12.6	1235	1024

TABLE XXXI

Difference between Hourly Rate of Excretion of Oxidized Ascorbic Acid in Overnight Specimen and Daytime Specimen on Control Day and Day of Cold Exposure

Date	Activity	Control				Supplemented			
		N	Mean diff.*	t	P	N	Mean diff.*	t	P
			mg./hr.				*mg./hr.*		
11–14F	Control (low activity)	40	0.0461	0.867	>0.05	43	0.1227	1.048	>0.05
25–26F	Cold exposure	32	0.5649	5.323	<0.01	43	4.5243	8.193	<0.01

* Mean difference was calculated by subtracting the overnight rate from the daytime rate. The fact that these values are positive indicates that the daytime rate was higher.

$$t = \frac{\text{Mean difference}}{\text{Standard error of mean difference.}}$$

The results of the determinations of oxidized ascorbic acid revealed no clear-cut diurnal trends. The most striking alteration in excretion of oxidized ascorbic acid occurred in relation with the outdoor cold exposure test (February 25–26). Table XXXI summarizes the difference in excretion rates between the overnight specimen and the daytime specimen for the control day and for the cold exposure day. It will be noted that the overnight and daytime excretion rates do not differ significantly on the control day, whereas on the day of cold exposure the rate of excretion during cold exposure is significantly higher than during the overnight collection period. These data indicate that exposure to cold produces an increase in the rate of urinary excretion of oxidized ascorbic acid.

Whole Blood Ascorbic Acid

The mean values for morning fasting whole blood ascorbic acid during the course of the experiment are listed with their respective standard deviations in Table XXXII. The determinations during week 1 were done on 4 separate days, one platoon per day, so that capsule administration had been in progress for from 1 to 4 days for the various platoons. By the third week the mean value in the supplemented group had risen to 1.7 mg. per cent and remained relatively constant until the end of the experiment, showing only a slight tendency for further rise. After one week of caloric restriction the mean value of the supplemented group reached 2.0 mg. per cent but then declined during the succeeding two weeks, reaching 1.74 mg. per cent at the end of the ex-

TABLE XXXII

Whole Blood Ascorbic Acid (mg. per 100 ml.)

Date	Activity	Control			Supplemented		
		N	Mean	S. D.	N	Mean	S. D.
3–4J	Morning fasting	39	0.638	0.288	42	0.584	0.257
7–10J	Morning fasting	41	0.580	0.335	44	1.050	0.651
7–10J	After 6 hr. low activity (control)	41	0.589	0.437	44	1.265	0.564
12–15J	Morning fasting	39	0.537	0.238	43	1.562	0.302
12–15J	After forced march	36	0.670	0.307	41	1.790	0.548
19–20J	Morning fasting	40	0.538	0.183	39	1.701	0.281
26–27J	Morning fasting	42	0.530	0.179	43	1.611	0.188
4–7F	Morning fasting	32	0.618	0.153	40	1.765	0.267
4–7F	After forced march	37	0.602	0.178	42	1.635	0.461
9–10F	Morning fasting	41	0.612	0.154	44	1.758	0.308
18–19F	Morning fasting	42	0.677	0.195	43	2.026	0.464
25–26F	Morning fasting	41	0.633	0.164	44	1.829	0.219
25–26F	After 4-hr. cold exposure	41	0.703	0.174	44	1.785	0.222
6–7M	Morning fasting	42	0.709	0.171	43	1.744	0.211
6–7M	After forced march	40	0.771	0.212	43	1.756	0.185

periment. The significance of this temporary rise during the early phase of caloric restriction is unknown and it is not possible to state with certainty whether the two events are causally related. The control group showed only minor fluctuations throughout the course of the experiment. The mean value before capsule administration in this group was 0.64 mg. per cent. It fluctuated between 0.53 and 0.71 mg. per cent, the latter value being the one observed at the end of the experiment.

The values for whole blood ascorbic acid in samples taken immediately after forced marches, cold exposure, or a control period of low activity showed no significant changes.

Blood Glucose

No important differences in blood glucose between control and supplemented groups were observed.

Hemoglobin

The values obtained from the hemoglobin determinations are presented in Figure 11. The mean values for the control and supplemented groups remained closely parallel throughout the study. During the first two weeks the mean value for the entire test company rose from 15.1 to 16.2 Gm. per hundred milliliters. This rise may reasonably be attributed to acclimatization to the altitude of the camp site (8310 ft. above sea level), and its magnitude is comparable to values given in the literature for persons residing at similar altitudes.[36,37] From the second through the sixth week the mean hemoglobin concentration of the entire test company remained relatively constant, showing only a slight tendency to decline. During the three weeks of caloric restriction both the supplemented and control groups showed a progressive rise in hemoglobin concentration, the mean values for the entire test company being 16.0 Gm. per cent at the beginning of caloric restriction and 17.0 Gm. at the end of the experiment. Because of the striking temporal relation between the period of caloric restriction and this second rise in hemoglobin, a causal relation between the two events appears likely; it cannot, however, be proved. Prolonged undernutrition is known to result in anemia. We have been unable to find information in the literature on the changes in hemoglobin concentration during the early phases of moderate caloric restriction.

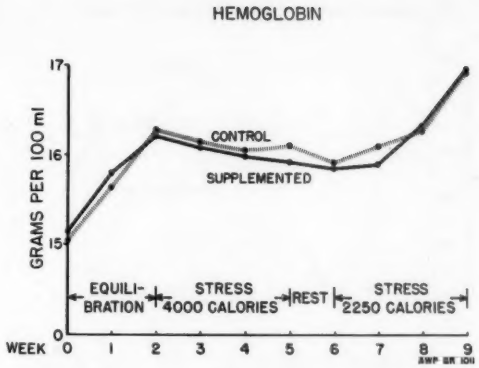

Fig. 11. Mean Hemoglobin Values of Test Subjects During the Course of the Experiment.

The rapidity of the rise suggests that this is a relative phenomenon related to a reduction in plasma volume. If one were to postulate an effective loss of vascular bed proportional to the loss of total body weight, it is seen that the 6.3 per cent mean increase of blood hemoglobin concentration compares favorably with the 5.8 per cent greater body weight at the beginning of this period than at the end. The long life of the erythrocyte would cause such an acute contraction in vascular volume to reduce the circulating plasma volume before it affected the corpuscular mass. Analysis of data from individual men, however, failed to reveal a significant correlation between change in body weight and change in blood hemoglobin concentration ($r = 0.029$). Seventeen per cent of subjects showed no change or a decrease in hemoglobin concentration while all subjects had a loss of body weight. The cause for this late rise in hemoglobin still remains obscure.

Eosinophil Counts

The variations in mean values for eosinophils in the morning fasting blood samples are presented graphically in Figure 12. The fluctuations that occurred are all within what is usually considered the normal range. There

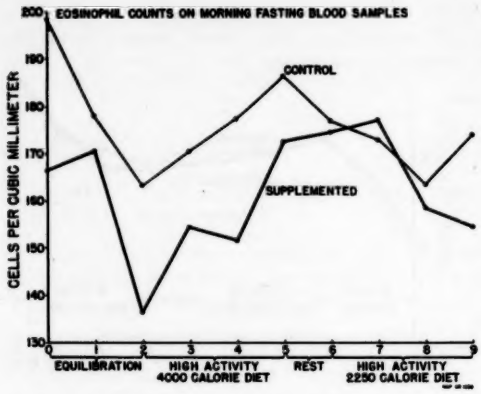

Fig. 12. Mean Eosinophil Counts of Morning Fasting Blood Samples During the Course of the Experiment.

were no important long-term trends and no striking differences between the two treatment groups. Table XXXIII summarizes the eosinophil count data on the days when a count was taken in mid-day after some type of activity, as well as a morning fasting count. Here the postactivity count is expressed as a percentage of the morning fasting count. It will be noted that no important change in eosinophil count occurred on the control day when 6 hours of low activity intervened between the morning fasting and postactivity counts. In contrast to this, on the days of the forced marches a profound fall in eosinophil count occurred on each of the 3 occasions when these observations were made. In each of the 3 forced marches the mean percentage value for the supplemented group was lower than the control group, indicating that the supplemented group showed a greater percentage fall in eosinophils.

Two analyses of covariance were carried out on the eosinophil data. In both, the mean per cent eosinophil values for the 3 forced marches were used as the variates. In the first analysis, the per cent eosinophil value on the control day (low activity) was used as a covariate (Table XXV, Analysis 4). The difference (control minus supplemented) between the means of the two treatment groups adjusted for covariance was 6.18 per cent, i.e., the control group's eosinophil count after the forced marches expressed as a per cent of the morning count was higher than the supplemented group's. The 95 per cent confidence limits of this difference are 10.92 and 1.44. The F ratio of the difference was 6.721, giving a P value of 0.02, indicating statistical significance at the 2 per cent level of probability.

In the second analysis of covariance, the absolute eosinophil count of the first morning fasting specimen of the experiment was used as the covariate (Table XXV, Analysis 5). The difference between the adjusted means was 4.79 per cent, with the control group again showing the higher mean value. The 95 per cent confidence limits of this difference are 9.58 and 0.00. The F ratio was 3.968, giving a P value of 0.05, indicating statistical significance at the 5 per cent level of probability.

In neither of these analyses of covariance was the regression of the variate on the covariate statistically significant.

It is of interest to note that no important change in eosinophil count occurred during the cold exposure test (February 25–26).

Creatinine

The data on creatinine excretion revealed no notable differences between the two treatment groups. No consistent alteration in creatinine excretion occurred in relation to the forced marches.

Uric Acid

After capsule administration was begun, the supplemented group usually had higher levels of uric acid excretion than the control group. It is probable that one or more of the vitamins in the supplement or metabolites of

TABLE XXXIII

Eosinophil Counts Expressed as Per Cent of Morning Fasting Control Count

Date	Activity	Control			Supplemented		
		N	Mean	S. D.	N	Mean	S. D.
7–10J	6 hr. low activity (control)	42	112.17	61.53	44	94.95	34.97
12–15J	Forced march	41	38.56	20.62	44	34.68	23.85
4–7F	Forced march	37	36.16	21.36	42	26.40	13.85
25–26F	4-hr. cold exposure	41	103.20	21.30	44	98.11	18.66
6–7M	Forced march	40	32.93	12.24	42	30.17	11.04

TABLE XXXIV
17-Ketosteroids

Date	Activity	Overnight		Daytime		Evening		Total (24 hr.)	
		Control	Supplemented	Control	Supplemented	Control	Supplemented	Control	Supplemented
		mg./hr.		*mg./hr.*		*mg./hr.*		*mg./hr.*	
6–10J	Control	0.49	0.48	0.58	0.61	0.53	0.75	0.56	0.62
11–15J	Forced march	0.50	0.50	0.52	0.63	0.54	0.58	0.51	0.56
25–27J	High activity	—	—	—	—	—	—	0.60	0.48
3–7F	Forced march	0.45	0.46	0.45	0.50	0.58	0.53	0.48	0.49
10–11F	Control	0.41	0.66	0.51	0.42	0.51	0.46	0.47	0.53
17–19F	High activity	—	—	—	—	—	—	0.50	0.46
27–28F	Forced march	—	—	—	—	—	—	0.45	0.45
5–7M	Forced march	0.30	0.33	0.37	0.38	0.40	0.43	0.34	0.37

these vitamins gave a reaction with the uric acid reagent. Ralli and co-workers[38] have shown that high levels of ascorbic acid in urine cause falsely high uric acid values. Because of the uncertainty of the uric acid determination under these circumstances, no further analyses of these data were made.

17-Ketosteroids

Determinations of 17-ketosteroids were made on composite specimens prepared by mixing a fixed percentage of the total volume of each urine specimen. There were two composite specimens for each platoon, one for the supplemented group, and one for the control group, for each period of urine collection. Samples were preserved with hydrochloric acid; they were packed in dry ice and shipped by air to the Laboratory in Chicago where the determinations were made. The results are summarized in Table XXXIV. There were no significant diurnal trends, nor were there any important differences between the two treatment groups. It is of interest to note that no consistent and clear-cut rise was seen in the specimens collected during or following the forced marches. The values for the last week for both treatment groups are somewhat lower than those of previous weeks. This may possibly be an effect of decreased caloric intake, since decreased 17-ketosteroid excretion has been reported in caloric restriction.[39]

Discussion

EOSINOPHILS AND COLD EXPOSURE

In the MNL study at Camp Shilo, Manitoba,[40] 32 men were exposed to a mean temperature of —35° F. for 3 hours during a truck ride. The mean eosinophil count was 117 per cu. mm. before the exposure and 101 per cu. mm. immediately after the exposure. On continued exposure to cold, the mean count fell to about 75 per cu. mm. This is in keeping with the failure in the present study to find a significant change in eosinophil count at the end of 4 hours of exposure to cold.

EOSINOPHILS AND CALCIUM PANTOTHENATE

Ralli and co-workers[41] found that subjects who had received 10 Gm. of calcium pantothenate daily for 6 weeks showed an elevation of fasting basal eosinophil count and a decreased eosinopenia on immersion in cold water. In the present study, the administration of a vitamin mixture containing 320 mg. of calcium pantothenate per day had no apparent effect on fasting eosinophil levels, and the eosinopenia following forced marches was slightly, but statistically significantly, greater than in the control group.

ASCORBIC ACID AND EOSINOPHIL FALL

Bacchus and Toompas[42] found that the fall in eosinophil count which occurs after injection of epinephrine in rats was prevented by pretreatment with 150 mg. of sodium ascorbate intraperitoneally. In the present study, the group of subjects receiving 1200 mg. of ascorbic acid per day showed a slightly greater eosinopenia after forced marches than the unsupplemented group.

COLD EXPOSURE AND BLOOD ASCORBIC ACID

In the MNL study at Camp Shilo[40] a

transient rise in serum ascorbic acid was observed in men exposed to extreme cold for 3.5 hours. More prolonged exposure led to a fall below the control levels. Ralli *et al.*[41] also observed a rise in blood ascorbic acid in men immersed in cold water for a short period of time. In the present study, the unsupplemented group exhibited a slight rise (0.07 mg. per cent) in blood ascorbic acid during 4 hours of cold exposure. This rise was statistically significant ($t = 3.72$, $P < 0.01$). The supplemented group showed a decrease of 0.03 mg. per cent during the 4-hour cold exposure.

URINARY ASCORBIC ACID AND COLD

Ralli *et al.*[41] observed in human subjects a rise in urinary ascorbic acid excretion during the 4-hour period following immersion in cold water. In the MNL Camp Shilo study, a slight increase in urinary ascorbic acid excretion occurred during the first day of cold exposure. In the present study, no significant change in urinary total ascorbic acid secretion occurred during 4 hours of cold exposure.

Monnier and Weiss[43] have reported that in rats exposed to an environmental temperature of 0° C. the urinary excretion of total ascorbic acid rose slightly and dehydroascorbic acid and diketogulonic acid excretion rose markedly. In the present study, a marked rise in the excretion rate of the oxidized forms of ascorbic acid was observed during a 4-hour period of cold exposure.

17-KETOSTEROIDS AND EXERCISE

We have been unable to find information on the effect of strenuous muscular activity on 17-ketosteroid excretion. Pincus and Hoagland[44] found an increase in excretion of 17-ketosteroids in men during flying which was directly proportional to the length of flying time, but this probably represents mainly a psychological stress. Venning and Kazmin[45] found an increase in urinary corticoids in Army recruits after a 4-mile route march; they did not study 17-ketosteroid excretion on these subjects.

17-KETOSTEROIDS AND ASCORBIC ACID

Kayahan[46] gave 4 Gm. of ascorbic acid per day for 4 days to 11 subjects and observed a marked decrease in urinary 17-ketosteroid excretion. The supplemented group in the present study did not show a decrease in 17-ketosteroid excretion.

SUMMARY

In a study on two groups of soldiers, one supplemented with high doses of vitamins of the B complex and ascorbic acid, the other receiving placebos, the following observations were made:

There were no statistically significant differences between the two groups in regard to urinary nitrogen excretion, blood glucose, hemoglobin, creatinine excretion, and 17-ketosteroid excretion. Urinary and blood ascorbic acid showed the expected differences between the treatment groups, with very high values in the supplemented group. A statistically significant increase in oxidized ascorbic acid excretion occurred in both groups during cold exposure.

The fall in eosinophil count during forced marches was statistically significantly greater in the supplemented than in the control group.

There was a statistically significantly greater fall in body weight in the supplemented group during the course of the experiment.

A group of psychological tests performed at intervals during the study did not reveal any differences between the two treatment groups.

ACKNOWLEDGMENT

The many individuals and organizations who gave assistance and advice in the conduct of this study are listed in the full report of the experiment.[47]

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Resumen

Efecto de la administración suplementaria de vitaminas en soldados residiendo en un medio ambiente frío. Parte 2. Determinaciones psicológicas, bioquímicas y otras

En un estudio de dos grupos de soldados, el uno suplementado por grandes dosis de vitaminas del complejo B y de ácido ascórbico, el otro recibiendo placebos, se hicieron las siguientes observaciones.

No hubo diferencias estadísticamente significativas entre los dos grupos en cuanto a la excreción urinaria de nitrógeno, glucosa en sangre, hemoglobina, excreción de creatinina y de 17-ketosteroides. El ácido ascórbico en sangre y orina mostró las diferencias atendidas

entre los grupos tratados, con valores muy altos en el grupo suplementado. Un aumento estadísticamente significativo en la excreción de ácido ascórbico oxidado ocurrió en ambos grupos durante la exposición al frío.

La caída del recuento de los eosinófilos durante las marchas forzadas fué mayor—a un grado estadísticamente significativo—en el grupo suplementado que en el grupo control.

Hubo una caída mayor en peso corporal en el grupo suplementado durante el curso del experimento.

Una serie de tests psicológicos cumplidos periódicamente durante el estudio no revelaron ninguna diferencia entre los dos grupos tratados.

REGULATED *versus* FREE DIET *in the Treatment of* DIABETES MELLITUS

By WILLIAM S. COLLENS, M.D.*

THE DISCOVERY of insulin 30 years ago had the natural effect of throwing into sharp focus the questionable importance of the regulation of the diet in the treatment of diabetes mellitus. While up to that time the control of diabetes rested purely upon restriction of those diet components causing glycosuria and hyperglycemia, the isolation of insulin made it possible for the diabetic to utilize carbohydrate as he had never been able to do previously.

It is interesting that while insulin was being introduced into general use, there were still some workers concentrating upon the development of diets which would make it possible for patients to be provided with their caloric needs, but which were restricted in carbohydrate content to minimal levels compatible with the prevention of ketonuria of dietetic origin.

Thus I can recall my visit to Banting in Toronto in 1923, when I saw the early liberalization of the carbohydrate fraction of the diet by Banting, Campbell and Fletcher,[1] while the medical literature of this period and some time later still carried articles by Petren,[2] Woodyatt,[3] Newburgh and Marsh,[4] and Shaffer,[5] in which diets with severe carbohydrate restriction were recommended. As a matter of fact, carbohydrate intake was reduced to a point which barely avoided the development of ketosis from the increased fat in the diet made necessary by the provision for an adequate caloric intake. At the same time, Allen was still advancing the virtues of diets causing conditions short of starvation, although he recognized the discovery of insulin as one of major importance.[6]

About five years after the discovery of insulin, it became apparent to some students of the subject that clinical improvement in the diabetic was better effected by liberalizing the carbohydrate content of the diet and increasing the dose of insulin to meet the need of this change. Thus, there appeared papers by Sansum and Blatherwick,[7] Geyelin,[8] Adlersberg and Porges,[9] and Rabinowitch,[10] all of them describing the benefits of what came to be known as the "high carbohydrate" diet. Their diets were designed to provide the patient with an amount of carbohydrate approaching the needs of the normal person. Thus diets containing 250 to 300 Gm. of carbohydrate became popular and appeared to achieve a good, practical, clinical result, especially in young or young adult diabetics. Patients were satisfied to the point which made it unnecessary for them to pilfer additional food. They felt well; their nutritional state improved; and, with the introduction of long acting insulins,[11] smoother control of the glycosuria and hyperglycemia was made possible.

Two things happened, however, to disturb what appeared to be a reasonably satisfactory dietary technique for the treatment of the diabetic.

First, there were some workers who felt that the employment of insulin should so correct the disturbance in carbohydrate metabolism in the diabetic as to make it possible for him to utilize unlimited quantities of car-

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bohydrate. Thus, in 1925, Blackfan and his group were already feeding their juvenile diabetics at the Boston Children's Hospital a "free diet," self-selected by the patient. Others who have proclaimed the virtues of unrestricted diets and have been concerned solely with the clinical well-being of their patients were Stolte,[12] Tolstoi,[13] and Lichtenstein.[14]

Secondly, more recently it became apparent to some investigators that a number of diabetics, if they lived long enough, were destined to develop certain complications or sequelae, regardless of the severity or degree of control of the diabetes. Thus Dolger pointed to the high incidence of retinopathy in diabetics of 10 or more years' duration.[15] It appeared to others also that the nephropathic picture originally described by Kimmelstiel and Wilson[16] as intercapillary glomerulosclerosis was similarly a sequel to which the diabetic was inexorably destined, regardless of the severity or degree of control of the diabetes. Thus, from a long-term standpoint, the question was naturally asked whether it made any difference if the patient's diabetes was well controlled.

These unsettled questions have therefore posed the important problem of determining what represents suitable management of the diabetic, and have burdened the physician with the responsibility of selecting one of two widely divergent philosophies to guide him in caring for this group of patients: Should the patient be treated with a "regulated diet" based upon certain known nutritional principles, or should he be allowed a "free," self-selected, unmeasured food intake? Let us examine this problem carefully.

The "Free" Diet

In 1939, Tolstoi and Weber published the results of their study which appeared to present some evidence to justify the use of the "free diet."[17] They found in their observations on 2 severe diabetics that the patients could be maintained in positive nitrogen balance if they were given sufficient insulin to utilize enough carbohydrate to spare protein. They felt that as long as the patient had a sense of well-being, was maintaining his weight, was in positive nitrogen equilibrium and free from ketonuria, then hyperglycemia and glycosuria, even of considerable magnitude, could be disregarded.

It is obvious that such a position must naturally make one conclude that dietary control and close and careful regulation of insulin dosage are unnecessary, and time- wasting for both the physician and patient.

I am reminded of an experience I had in 1930 when I wrote a *Manual for the Jewish Diabetic* which contained diets and recipes that historically appealed to the Jewish palate.[18] Because of my respect for Banting and my feeling that my small opus might serve as a contribution to his library on diabetic literature, I sent him a copy with my compliments. I received a very warm acknowledgment from him in which he stated "I may say that the whole thing looks very complicated and difficult. I would very much hate to be a diabetic and have to learn all about insulin and diets. I am perfectly certain that were I a diabetic patient, I would go to the doctor and tell him what I was going to eat and relieve myself of the worry by demanding of him a proper dose of insulin."

Let us now explore the validity of such conclusions.

It seems to me that before embarking on a plan of treatment one should have clear in his mind what he aims to accomplish. It is certainly a self-evident truth that the function of the physician is to relieve suffering; that if he is confronted with a patient suffering from an incurable painful carcinoma, his role is discharged in relieving the patient of his pain, and that if he is treating a patient with pneumococcus pneumonitis, his role consists in employing those measures, such as antibiotics and chemotherapeutic agents, which will eliminate the disease and return the patient to a normal state.

So it is with treating the diabetic. In studying the written accounts of authors of monographs and textbooks on the treatment of diabetes mellitus and from my own experience with diabetics for a period of 30 years, I feel that a rational aim of treatment should be to establish a physiologically metabolic equilib-

rium, restoring as far as is practically possible the conditions for the utilization of foodstuffs equal in quantity and in kind to those which the nondiabetic consumes, and to employ those measures which so far as is known will protect the patient against the complications and sequelae of this disease.

This therefore entails the provision of:

1. A diet supplying the physiological needs of the body for carbohydrate, protein, and fat.
2. Insulin in such quantities and such form as most efficiently to aid in the utilization of the available carbohydrate.
3. Provision of the physiological needs for water, electrolytes, and vitamins.
4. Freedom from hypoglycemia.

When these aims are accomplished, then the following are natural corollaries:

1. The patient experiences a sense of "well-being."
2. His weight is satisfactorily controlled through dietary regulation—an important part of the physician's responsibility.
3. Minimal glycosuria is effected.
4. The fasting blood sugar and, for that matter, the prandial blood sugars are maintained within limits close to normal.

It is most interesting that such regulation is just as easily accomplished as the random haphazard control effected by the "free diet." It is most unfortunate that the uninformed physician is willing to accept the "free diet" as satisfactory—first, because he is relieved of the unpleasant chores of diet calculation and instruction of his diabetic patients; and second, because he accepts rather uncritically apparently authoritative assertions that no harm can come of it.

While Tolstoi attempts to classify these two schools of therapy as clinical control versus chemical control, he apparently intimates that those who seek to establish good chemical control disregard clinical control. That is far from correct. In seeking an ideal formula for treatment, it becomes evident that the clinical improvement of the patient is certainly the state to be achieved. I would much prefer to differentiate these two methods of therapy as "good control" versus "haphazard control." In my opinion, the free diet is not good therapy, for a number of reasons, as discussed below.

Disadvantages of the Free Diet

(1) It has been indisputably demonstrated that glycosuria is accompanied by diuresis with the loss of water and electrolytes, which may be of sufficient magnitude to produce dehydration of body tissue.[19] There is recent evidence to show that hyperglycemia also is accompanied by increasing loss of water and electrolytes.[20]

It is interesting that diuresis can exist without the patient being aware of it. I have seen the untreated diabetic disclaim any thirst on questioning until his diabetes had come under control, after which he has revealed that polydipsia had ceased and that he had previously imbibed large quantities of water purely because he liked water. This only demonstrates how careful one must be in evaluating subjective symptoms.

(2) Failure to follow the content of glucose in the blood and fractional urine specimens can result in failure on the part of the physician to detect the presence of asymptomatic hypoglycemia. I have seen experimentally induced insulin hypoglycemia in dogs and humans result in blood sugars as low as 40 mg. per 100 cc. without any clinically detectable evidence of the hypoglycemic state. There is little question of the dangers of such a condition, particularly when one is guided solely by the subjective well-being of the patient. Furthermore, by failure to integrate diet regulation with insulin therapy, especially protamine zinc insulin, it is possible for the patient to experience considerable prandial glycosuria, and be hypoglycemic in the postprandial period. The insulin reaction is particularly fraught with danger in the elderly. Intracranial vascular accidents, transitory pathological alterations in the electrocardiograms, coronary thrombosis, miliary cerebral hemorrhages, and irreversible coma have been reported to occur during insulin hypoglycemia.[21] Its effect upon secretion of epinephrine and anterior pituitary hormones has also been documented.[22] Thus, hypoglycemia can provoke rebound hyperglycemia and lead to instability of the diabetes.

It is obviously dangerous to depend upon the patient's subjective reports on experiences with hypoglycemia. The physician can more easily control this problem if he follows the glucose content of the blood and urine with regularity.

(3) One of the most important complications to which the female diabetic is vulnerable is pruritus vulvae. There are few complications that are more common or which can be more serious. I have seen severe pruritus vulvae produce such violent distress as to cause the patient to threaten suicide. The significant feature of this complication is that it is entirely preventable. It has been demonstrated by Greenwood that pruritus vulvae frequently results from tricophyton infection of the labia.[23] These organisms are known to thrive in the rich glucose medium on the vulval tissues of glycosuric females because some of the urine drops are left on the vulva during micturition. The condition is often dramatically relieved within 24 to 48 hours by making the patient aglycosuric. Sometimes frequent vulval irrigations and the local application of 3% ammoniated mercury ointment are necessary. In more stubborn cases, local exposure to x-ray therapy will be required. The fact remains, however, that this important complication is attributable to the presence of the glycosuria and is preventable by rendering the urine sugar-free.

Interestingly, too, the condition is transmissable. Pruritus of the glans penis has occurred, and the presence on it of glucose and tricophyton have been detected after sexual relations with a glycosuric female with pruritus vulvae.

(4) Tolstoi has indicated, among his arguments against diet regulation, that it produces unfavorable conditioning, especially in child diabetics, and that these patients tend to become neurotic and develop a "dietary complex." This is not borne out in actual practice. Sherrill states that in 35 years he has not encountered any patient in many thousands who developed a psychoneurosis as a result of having to adhere to a regulated diet.[24] I, too, have never been disturbed by this problem. This is also the experience of those who see diabetic children in summer camps devoted exclusively to their care.

On the contrary, I can well imagine intelligent diabetics being greatly disturbed when advised by a physician that they need no diet regulation, may eat as they please, and may totally disregard the fact that they are diabetics, provided that they are treated with insulin. My experience teaches me that a diabetic is conditioned to expect dietary advice from his physician. Furthermore, he wants to be told what to eat rather than what not to eat.

(5) It may be stated that the severity of a patient's diabetes is dependent upon his capacity to utilize carbohydrate.

In the untreated diabetic, a severe reduction in carbohydrate tolerance is accompanied frequently by incomplete and excess oxidation of fats, so that besides the clinical manifestations of dehydration and acidosis, the tell-tale laboratory evidence of acidosis becomes apparent with the accumulation of acetone in blood and urine and a reduction in base, chlorides, and CO_2 combining power of the blood. However, in the absence of ketosis in the insulin-treated diabetic, the severity of the impaired capacity to utilize carbohydrate can be determined only from knowing how much carbohydrate is ingested, and how much glucose is excreted, the balance presumably representing the quantity utilized by the body. Such a balance study provides the physician with some basis for establishing individual carbohydrate tolerance and determining the insulin dose.

While insulin causes a rise in the respiratory quotient, a depression in the blood sugar, and a disappearance of sugar from the urine, these are only the laboratory guides to indicate that an increase in glucose utilization has occurred during the period of action of the insulin. Although the function of insulin is to increase the capacity of the organism to utilize glucose, it is apparent from experience that some diabetics require a significantly larger dose of insulin with a comparable quantity of carbohydrate than do others. Thus patient A might need 100 units of insulin to aid in the utilization of 200 Gm. of available glucose in the

diet, compared with patient B who could accomplish the same feat with 20 units. The recognition of a specific relation between glucose utilized and insulin injected was originally conceived by Geyelin and served as a useful index in indicating the severity of the diabetes.[8]

Since patients vary in their capacity to utilize carbohydrate, and also vary in the number of grams of glucose utilized per unit of insulin, the size of the insulin dose can be established individually only on the basis of the expected consumption of a measured quantity of available glucose per unit of insulin. Thus, in the example just cited, it is seen that patient A can utilize only 2 Gm. of glucose for each unit of insulin administered, as compared with patient B who can dispose of 10 Gm. of available glucose per unit of insulin injected.

It is apparent that one cannot satisfactorily direct the use of insulin without integrating positive dietary instructions. This becomes even more evident when one considers the variety of available insulins, including short acting, long acting, and intermediate acting, each one having a pharmacodynamic action in which the peak of its blood sugar lowering effect is placed at a different period in a time curve.

To prescribe insulin on any other basis is to me a haphazard, hit and miss technique. Furthermore, it seems to me that a substance as potent and as dangerous as insulin should not be given without providing dietary instructions both with regard to the quantity of food to be ingested and the time of feeding. This is diet regulation. A patient who eats what and when he pleases, guided by his whims and his appetite, is prey to inordinate glycosuria or unpredictable hypoglycemic states. Furthermore, failure to examine the blood and urine of the diabetic under care must of necessity result in failure to recognize that partial remissions may occur in this disease, necessitating a reduction in insulin dosage.

(6) There is no evidence to indicate that hyperglycemia is an entirely innocuous state. Lukens has demonstrated that the persistent intraperitoneal injection of glucose in cats with an effectively maintained hyperglycemia, results in irreversible hydropic degeneration of the islets of Langerhans.[25] Young had even earlier demonstrated that hyperglycemia and islet degeneration followed the injection of anterior pituitary extracts into dogs.[26]

However, there is considerable disagreement among clinicians whether persistent hyperglycemia in the human has any long-term deleterious effect. Tolstoi, for example, does not believe that experimentally induced hyperglycemia in the animal has the same significance as the hyperglycemia in the diabetic receiving insulin, but he presents no proof to support his opinion. On the other hand, Jackson and his associates find that good control of the diabetes in children has delayed and may possibly prevent the degenerative lesions considered characteristic of long standing diabetes.[27] Here too, however, the evidence is not definitive.

Even if the evidence of the deleterious effects of hyperglycemia were less convincing, why permit it to exist when it can be easily avoided? Does it not ring true to try to restore those conditions that can be measured quantitatively to normal levels? Does not one set his sights in the treatment of essential hypertension on restoring the blood pressure to normal? Certainly there is no convincing evidence that a successful reduction in blood pressure in a case of hypertension removes those factors that make for serious arterial degeneration. Yet, that is our aim on the basis of our present knowledge of the disease.

Diabetic Complications

We now come to the argument that close chemical control of diabetes is of only dubious value since it has been observed that diabetics of 10 or more years standing are destined to develop nephropathic and retinopathic changes whether or not the diabetes is well controlled. There is a wide difference of opinion on this.

The findings of Jackson and his group have already been noted. These authors also observed that the growth of diabetic children is normal or above average normal when the diabetes is well controlled, but below normal with poor control.[28]

Keiding and his associates have recently reported the results of their observations on 451 patients studied in the Joslin Clinic.[29] While they noted that the incidence of degenerative vascular disease was greater in the group whose diabetes was of 20 or more years' duration, they indicated that it was equally influenced by the degree of control of the diabetes. Those whose diabetes was under good or excellent control showed a significantly lower incidence of nephropathic and retinopathic complications than those classified as having fair or poor control. It is interesting that of the 451 patients studied, 390 were regarded as having poor or fair control of the diabetes. The authors did not believe that the age of onset of the diabetes or severity of the disease were significant factors.

However, Siegel and Allen have observed that Kimmelstiel-Wilson lesions in the kidney were found particularly in patients with relatively mild diabetes.[30] Similarly, Zubrod and his associates more recently reported their observations that diabetics, who came to postmortem examination and had Kimmelstiel-Wilson lesions, showed during life a progressive reduction in insulin needs in the closing years of life.[31] It appeared to these authors that control of the diabetes with reduced insulin dosage was presumptive evidence that these patients became milder diabetics, in whom the diabetes was more easily controlled. They further observed the virtual absence of acidosis throughout the entire duration of the diabetes, and therefore further stressed the relative mildness of the diabetes in these cases.

My own observations are not in entire conformity with those of Keiding and his group. I have been following 9 patients with mild diabetes whose insulin requirements are less than 15 units per day, in whom the urines are almost continuously free of sugar, the fasting blood sugars close to normal, and the dietary intake approximating physiological needs; and yet these patients show evidence of progressive nephropathic and retinopathic degeneration. This large number of well-controlled mild diabetics found in 65 observed patients having diabetic nephropathy curiously does not appear in Keiding's series. It at least leaves me with the suspicion that the degree of control of the diabetes may not be a definitive factor in the development of these complications.

Furthermore, there is no convincing evidence that the duration of the disease is a sole factor. Although Dolger has indicated the almost universal retinopathic degeneration which occurs in diabetics of 10 or more years standing, Keiding and his group point to the large number of diabetics of long standing who have fortunately escaped this dread complication. On the other hand, I can point to several young diabetics under the age of 25 who have developed nephropathy and retinopathy less than 2 years after the discovery of the diabetes, one young college student of 18 showing evidence of these complications 6 months after the onset of his diabetes. Dolger and Tolstoi do not believe that the degree of control of the diabetes has any effect upon the ultimate development of vascular degenerative changes. Tolstoi thinks, therefore, that close, chemical control is a time-wasting, effort-wasting method that brings no greater good.

The argument, however, that it makes no difference how accurately the diabetes is controlled, since either closely regulated management or loose, haphazard management lead to the same end result, does not appear to me to be entirely valid. It would presuppose that complete and ideal control of diabetes lies only in the use of a diet and the injection of insulin. However, I am not convinced that this is altogether the case.

Other Facets of Diabetes

It is my impression that diabetes mellitus may be a disease possessing many facets, of which a disturbance in insulin function represents only one small part. There is evidence to indicate that the clinical picture of the disease results from additional disturbances in other enzyme systems unrelated to or affected by insulin function.

If that proves to be the case, then one should regard many of the degenerative changes occurring in the disease, not as complications, but as collateral phenomena comprising a component part of the disease itself. Thus, from a therapeutic standpoint, one could regard the

role of insulin as one of correcting a disturbed enzyme system which would make possible the utilization of normal carbohydrate needs, but playing no part in correcting disturbed correlative disorders. Then the administration of insulin would not in itself provide the entire answer to the complete control of diabetes.

I refer, for example, to the coexistence of peripheral neuropathy in diabetics. We have recently detected an impairment in the transmission of vibratory sense impulse in such a large number of diabetics as to indicate that it is almost an integral part of the disease.[32] We have observed that 94 per cent of all diabetics, whether or not they have neuropathic symptoms, have an impairment in transmission of vibration sense through the terminal parts of their extremities. This was established in a study made with an electrically driven tuning fork in which the amplitude of vibration could be varied, thus making it possible to quantitate the intensity of impairment in vibratory sense.

Since certain vitamins such as thiamine pyrophosphate, niacin, pyridoxine and riboflavin are intimately related to nerve function, it would be reasonable to expect that a disturbance in the function of these coenzymatic factors may play a role in the clinical picture of the diabetic syndrome.

Furthermore, we have reported our observations indicating that those diabetics with proteinuria and retinopathy have a strikingly greater degree of vibratory sense impairment than diabetics free from these disorders.[33] This interesting co-existence of more advanced neuropathy in diabetics with proteinuria leads to the question as to whether the condition that makes for a disturbance in the metabolism of the peripheral nerve also makes for structural alterations in kidney and retina. If that is so, then one may speculate on the possibility that certain enzyme systems, possibly involved with fractions of vitamin B complex, are disturbed collaterally with a disordered insulin function in diabetes mellitus. If such independent factors exist, making diabetes a disease with multiple enzymatic disturbances, then one cannot expect the use of insulin alone to do more than correct the disorder in carbohydrate metabolism; its administration would have no effect in preventing these collateral clinical disorders. The statement, then, that it makes little difference from a long range view how well one controls hyperglycemia and glycosuria is not logical.

Is it not safer to say that we do not know all the answers and that further investigations may ultimately yield the elucidation of all the components that make up this complex disease known as diabetes mellitus, so that diet and insulin may then be supplemented by additional therapeutic agents to provide for complete and protective treatment of the diabetic?

Summary

The discovery of insulin had a marked impact upon our ideas about the role of diet in the management of the diabetic. While it naturally allowed for a liberalization of the diet to the point where patients could be provided with their physiological needs for carbohydrate, one school of workers further concluded that it was no longer important to regulate the diet of the diabetic at all and that he should be allowed a free, unrestricted, self-selected food intake.

When one seeks a rational basis for the treatment of the diabetic, that is, to create those conditions in the utilization of foodstuffs which would restore a physiological metabolic equilibrium without endangering the patient with the toxic effects of insulin overdosage, then the advantages of diet regulation become apparent in the form of clinical well-being, weight control, minimal glycosuria, approach to normal glycemia, and freedom from hypoglycemia. While the long-term benefits in the form of protection against degenerative vascular changes, nephropathy and retinopathy are not definitively proved, there are some investigators who find this to be the case.

The disadvantages of a free, self-selected diet are seen in the complications arising from unrestricted glycosuria, hyperglycemia, hypoglycemia, and haphazard insulin dosage.

In the argument that regulation of the diet and diabetes control play no part in the ultimate destiny of the diabetic, there should be more accurate identification of "control" as

we understand it today. There appears to be evidence to indicate that diabetes mellitus is a complex disorder in which there occurs a disturbance not only in carbohydrate metabolism, but also in other enzyme systems unrelated to and unaffected by insulin function. This would mean, then, that one should not expect the use of insulin alone to provide the entire answer to the complete control of the diabetic. If that is the case, it does not appear logical to abandon those dietary techniques which make possible a more scientific use of insulin; instead, we should continue our search for those components that may prevent and reverse the collateral phenomena which we recognize as nephropathy, retinopathy, and arterial degeneration.

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Resumen

Dieta controlada contrapuesta a dieta libre en el tratamiento de la diabetes mellitus

El descubrimiento de la insulina modificó de modo importante nuestros conceptos del papel de la dieta en el control del diabético. Al mismo tiempo que permitió la liberalización de la dieta hasta fornecer a los pacientes sus requerimientos fisiológicos de hidratos de carbono, se formó una escuela de trabajadores quienes concluyeron que ya no era necesario arreglar en nada la dieta del diabético, y que había que permitirle una libre y no restringida autoselección de alimentos.

Cuando se busca una base racional para la terapia del diabético—es decir, la creación de aquellas condiciones para la utilización de los alimentos que restituyan el equilibrio metabólico fisiológico sin poner en peligro al paciente por los efectos tóxicos de un exceso de insulina—entonces se vuelven aparentes las ventajas de la dieta controlada, en forma de bienestar clínico, estabilización del peso corporal, glucosuria mínima, glucemia casi normal, y eliminación de la hipoglucemia. Mientras que los beneficios remotos—en forma de protección contra las alteraciones vasculares degenerativas, la nefropatía, y la retinopatía—no quedan definitivamente demostrados, hay investigadores que consideran que el caso es así.

Los inconvenientes de una dieta libre y autoseleccionada aparecen en las complicaciones que traen su origen de la glucosuria no controlada, la hiperglucemia, la hipoglucemia, y la administración descuidada de la insulina.

En alegar que la regulación de la dieta y el control de la diabetes no juegan ningún papel en el destino ulterior del diabético, hay que identificar con más exactitud lo que es el "control" como hoy lo entendemos. Parece exista evidencia indicando que la diabetes mellitus es un desarreglo complicado en el cual ocurre un disturbio no sólo del metabolismo de los hidratos de carbono sino también de otros sistemas enzimáticos no relacionados con ni afectados por la función insulínica. Esto quisiera decir, pues, que no se debe atender del uso de la sola insulina la solución cabal al problema del control absoluto del diabético. Si tal fuese el caso, no pareciera lógico abandonar esos métodos dietéticos que posibilitan un empleo más científico de la insulina; al contrario, hay que perseverar en nuestra busca de los factores que puedan prevenir y revocar esos factores accessorios que reconocemos como nefropatía, retinopatía, y degeneración arterial.

Engineering or Understanding?

"If the human body is a machine and if the doctor is a technician appointed to overhaul and maintain it, to investigate its faults and put them right, the more he is confined to accepted methods of investigation and to the use of the latest tools and the most approved techniques of repair, the better. If, however, man is a creature of infinite variety, if every human being differs from every other in his inherited tendencies, his nutritional needs, his durability, his reaction to environmental deficiency and stress, and if each individual may change in any of these respects at any time for no apparent reason, then the doctor who must advise him when well and care for him when ill can work to no set rules and must be no yes-man."

—Sir Heneage Ogilvie. *The New Zealand Medical Journal* 52: 322, 1954.

Editorial

New Nutritional Standards

The Food and Nutrition Board of the National Research Council published the first table of recommended dietary allowances in 1943. The intake levels were designed for the maintenance of good nutrition of healthy persons in the United States under the conditions existing at that time. The recommendations were not proposed as optimal levels of intake, because our present state of knowledge does not permit a statement as to the optimum levels; nor were these meant to be permanently fixed, because the values were considered tentative or approximate.

Based on this yardstick, many very significant nutritional studies were performed and could be compared. The third revision, 1953, includes several important changes.

Again, it should be clearly understood that the levels of intake recommended are those which, in the judgment of the members constituting the board, are merely desirable goals toward which to strive in planning diets and food supplies. They are not requirements, because they represent more than the minimal needs to prevent overt dietary deficiencies. In many instances the nutrient intakes are higher than the average requirement for the healthy individual but lower than the amounts usually needed in disease states or in the following rehabilitation period.

Perhaps the most important change is a new method of calculating the estimates of caloric requirements.* The present system takes into consideration factors of sex, age, body size, and climate, as well as activity.

The method of calculation is as follows: Reference is made to the "standard" man or woman; that is, a person twenty-five years old, living in a temperate climate, with a body weight of 65 kilos for the man and 55 kilos for the woman. This standard person is engaged in moderate physical activity—neither sedentary nor indulging in excessive physical exertion. Examples might be light industrial worker, painter, delivery man, or a woman who is an active homemaker or a shop sales person. On the basis of eight hours of physical activity and four hours of sedentary activity in a mean environmental temperature of 50° F., the standard man would need a total caloric intake of 3200. Similarly, the standard woman would need 2300. At age forty-five, the caloric requirement for the man drops to 2900; and at sixty-five years of age, it drops further to 2600. In each case the calculation is based on the same height and weight. In the case of women, for the same age groupings the caloric recommendations are 2100 and 1800.

Similarly, when there are changes in weight, an allowance is made on the basis of the alterations from the standard weight, so that whereas it is recommended that the 65-kilo man get 100 per cent of the caloric allowance, it becomes 111 per cent if he weighs 75 kilos and 89 per cent if he weighs 55 kilos. In the case of women, it is 113 per cent for a 65-kilo woman, as compared with the 55-kilo standard, and 86 per cent of the total calories for the 45-kilo woman.

One deducts from the caloric requirement 5 per cent for an additional ten years of age above the standard, and also 5 per cent for a

* Shank, R. E.: Revisions of the Recommended Dietary Allowances *J. Am. Dietet. A.* 30: 105, 1954.

mean external temperature 10° higher than the standard. That is, for each 10° C. increment in mean enviromental temperature, one calculates a decrease of 5 per cent in the caloric requirement.

Caloric allowances are estimated on ideal weight and not on actual body weight.

In the third trimester of pregnancy, 400 calories are added. The caloric requirement during the earlier period of pregnancy is relatively unimportant. Lactation, on the basis of 850 ml. of milk daily, adds 1000 calories to the requirement.

One interesting development is the reduction in the calcium allowance from 1 Gm. to 0.8 Gm. per day. The allowances for iron and vitamin A remain unchanged. The previous system of allowing 0.5 mg. of thiamine per 1000 calories was continued, since it seems to provide a desirable margin of safety.

The recommended level of ascorbic acid is three to five times that needed for protection against gross scurvy, but it was decided that these earlier recommendations should be reaffirmed and retained in the new list.

One other significant development has been the acceptance of certain nutrients—vitamin B_6, biotin, pantothenic acid, and vitamin B_{12}—as essential nutrients for man. However, at this time no quantitative allowances are given.

S. O. WAIFE

Making of an M.D.

"The entrant to medicine must be picked for his ability, his enterprise and his integrity. I should like to add, though I fear to do it in these days, when every man is as good as every other only better, that he should be picked for his cultural, social and biological background. He should in his training be taught the whole store of knowledge of the past, that is, he should be securely grounded on orthodoxy. He should be tested mercilessly before he is sent out to practice. But when he is finally approved, he must be allowed the complete freedom of an individual. He will meet many puzzles; he must worry them out by the light of his previous experience, and he must act in any way he believes to be right. He will be consulted by his patients about their spiritual, domestic and business troubles as well as about their illnesses, and because the troubles of the mind and those of the body are inextricably interlinked, he must do his best to help and his advice must come from his own knowledge and experience and not merely reflect the voice of authority."

—Sir Heneage Ogilvie. *The New Zealand Medical Journal* 52: 322, 1954.

Jealous Specialists

"Much of the eccentric path traced by human progress has...been due to the basic law that the wrong idea sponsored by the right person has a better chance of gaining acceptance than the right idea sponsored by the wrong person. For all human beings are conservative and flock together into little, secure groups, with each group closing its ranks in the face of threats from other groups. It is a truism that to the shoemaker shoes are all and shoes are perfect, with a perfection which can be improved upon only by shoemakers. Shoemakers, therefore, are somewhat uncritical of shoes, but when a carpenter, seeing shoes with an unbiased eye, is cogently critical, his criticisms are brushed aside, however valid they may be. In compensation, however, the shoemakers will tolerate considerable eccentricity in shoemaking from one of their own professional group.

"For 'shoemaker' read 'physician or surgeon,' and for 'carpenter' read 'surgeon or physician.' Then look and understand the devious ways of advance in the medical arts and sciences!"

—*The Medical Press* 231: 239, 1954.

Dietotherapy

THE BLAND DIET

By CORINNE H. ROBINSON*

A DIET DESCRIBED as "bland" is one in which the choice of foods is restricted to those which are smooth and soothing in effect. By contrast, mechanical, chemical, and thermal irritation to the mucous membranes is avoided. The bland diet is useful in many disturbances of the gastrointestinal tract such as peptic ulcer and chronic ulcerative colitis. A basic plan is described in this paper and may be adapted to a variety of needs.

CHARACTERISTICS OF THE BLAND DIET

The bland diet may be planned to achieve the following objectives: (1) establish and maintain nutritional balance for all essential nutrients; (2) prevent mechanical irritation of the gastrointestinal tract; (3) reduce gastric acidity by inhibiting secretion and by neutralizing or diluting the gastric contents; and (4) be acceptable to the patient.

Fiber Content

The bland diet is restricted in its fiber content because it is believed that coarse fibers may irritate sensitive mucous membranes. The skin, seeds, and cellular structure of plant foods constitute the chief sources of fiber in the diet. The amount of fiber depends not only upon the kind of plant but also upon the degree of maturity. For example, celery is known for its fibrous nature, whereas white potato and carrots, when skins are removed, contain a minimum amount of fiber; young green beans contain small amounts of soft fiber, whereas mature green beans contain sufficient amounts of woody fiber so as to characterize them as being tough.

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The fiber content of the normal diet may be reduced by these progressive stages: (1) selecting only those varieties of foods known to be low in fiber; (2) using tender young vegetables rather than those which are overripe; (3) avoiding the skins and seeds of vegetables and fruits; (4) allowing only cooked vegetables and fruits, since cooking softens and disintegrates the fiber; and (5) puréeing fruits and vegetables and using only refined cereal foods.

Meats contribute fiber in the form of indigestible connective tissue; thus the tenderness of meat is dependent upon the amount of connective tissue which is present. This in turn is affected in part by the age of the animal from which the meat comes, and in part by the degree to which the muscle has been exercised. Tender cuts such as chops, steaks, oven roasts, and chicken may be used without chopping or grinding. Fish contains very little connective tissue and may be used without chopping.

It is not always appreciated that many less tender cuts of meat are equally well tolerated if they are suitably prepared. Cookery with moist heat at low temperatures results in changing the collagen to gelatin without toughening of the proteins. Pot roasting and stewing may be used for the more economical cuts of meat; usually the liquor in which these meats are cooked is not served to the patient.

Few diets are less well accepted than those in which fruits and vegetables are all cooked and puréed, meats are all ground, and cereals are cooked and strained. Undoubtedly, these drastic restrictions are necessary at times, but rarely is it necessary to continue them for a prolonged period. Present trends are in the direction of a more liberal diet which permits tender cooked vegetables and fruits of low-

fiber content and tender meats. It is pointless to insist upon the puréed foods if the patient refuses to eat them; indeed, such refusal will jeopardize good nutrition.

Flavor

Strongly flavored or "gas-forming" vegetables such as onions, broccoli, cabbage, turnips, and others are usually avoided. Overcooking of such vegetables results in the release of irritating sulfur compounds, but the decomposition products can be kept at a minimum if the vegetables to be cooked are heated quickly in order to destroy the enzymes which facilitate breakdown of the sulfur compounds.

Whether the stimulation of gastric acidity brought about by nonprotein nitrogenous substances such as creatine, purines, etc., or by highly seasoned foods is sufficient to cause harm has not been clearly determined. Some persons do experience discomfort following the use of such items in the diet. Customarily, meat soups and gravies are omitted from the bland diet if it is to be used in the treatment of peptic ulcer. Likewise, relishes, catsup, mustard, pepper, horseradish, and numerous other highly seasoned foods may be contraindicated. On the other hand, moderate amounts of salt and such spices as nutmeg and cinnamon lend interest to foods without undue stimulation. Discretion in the choice of foods and in the amount of seasoning used, rather than complete omission, would appear to be the sensible course to follow.

Reduction of Gastric Acidity

When the bland diet is used for peptic ulcer it is essential that gastric acidity be reduced. In the absence of anxiety and tension, the proper choice of food can result in a diminished flow of gastric juice or neutralization of the gastric juice or both. Fats are well known for their inhibitory effects on the gastric secretion, but their choice is restricted to those which are highly emulsified, such as are found in whole milk, cream, butter, and egg yolk.

Protein foods are effective in neutralizing the acid of the stomach. Milk has especially high buffering properties and becomes a basic food upon which the bland diet is planned. Meat, poultry, fish, and eggs are likewise useful for their neutralizing properties.

Intervals of Feeding

The bland diet may be given in three meals of moderate size together with smaller feedings at midmorning, midafternoon, and bedtime. The use of frequent feedings serves to dilute the stomach contents when that is desirable and, for some persons at least, results in more nearly adequate intake of nutrients.

Nutritive Adequacy

The patient who has been ill for some time may be suffering from a variety of deficiencies occasioned by an inadequate intake of nutrients because of undue dietary restriction. Many diets used for the treatment of peptic ulcer have been seriously inadequate in protein, iron, ascorbic acid, and thiamine. Disease itself may impose additional demands, as in the healing of tissue, or to compensate for poor absorption.

Long dependence upon a milk and cream diet, as used in some ulcer regimens, results in deficient intake of protein at a time when greater than normal levels are desirable for prompt healing. The omission of milk, on the other hand, as in some plans for the treatment of ulcerative colitis, can be equally debilitating if the intake of other protein foods is not correspondingly increased. Particular emphasis should be given to the inclusion of milk, eggs, meat, poultry, and fish; nonfat milk solids are useful in supplementing the protein intake when deficits must be corrected.

The iron content of restricted diets is likely to be low. Moreover, the use of alkali therapy may interfere with the absorption of dietary iron; supplementary iron is frequently indicated.

The belief that citrus juices may irritate mucous membranes is widely held, but even momentary discomfort can be avoided when such juices are taken at the end, rather than at the beginning, of the meal. Two servings should be included daily, since cooked vegetables and fruits cannot be relied upon to supply the necessary vitamin C. Thiamine can be provided in adequate amounts if en-

TABLE I

Nutritive Value of a Basic List of Foods for the Bland Diet*

Food	Household measure	Weight	Energy	Protein	Fat	Carbohydrate	Minerals		Vitamins				
							Ca	Fe	A	Thiamine	Riboflavin	Niacin	Ascorbic Acid
		Gm.	*cal.*	*Gm.*	*Gm.*	*Gm.*	*mg.*	*mg.*	*I.U.*	*mg.*	*mg.*	*mg.*	*mg.*
Milk	1 quart	976	670	34	38	48	1152	0.8	1,560	0.36	1.68	1.2	12
Eggs	2	108	150	13	12	Tr	52	2.6	1,100	0.10	0.28	Tr	0
Meat, poultry, or fish	4 ounces (raw wt.)	90 (cooked)	275	21	21	0	8	2.7	1,710†	0.22	0.30	5.2	0
Enriched fine cereal	1/2 cup	30 (dry wt.)	110	3	Tr	24	12	0.9	0	0.16	0.05	1.0	0
Enriched white bread	4 slices	100	275	9	3	52	79	1.8	0	0.24	0.15	2.2	0
Potato	1 medium	150	125	3	Tr	29	17	1.0	30	0.14	0.05	1.5	21
Cooked leafy, green, or yellow vegetable	1 serving	100	30	2	Tr	6	44	1.0	3,180	0.08	0.08	0.7	15
Cooked vegetable	1 serving	100	35	1	Tr	7	19	0.6	660	0.06	0.06	0.6	3
Citrus fruit	2 servings	200	90	2	Tr	24	54	0.8	240	0.14	0.06	0.4	94
Other fruit	2 servings	200	125	1	1	32	24	1.0	1,200	0.08	0.08	0.8	8
Butter or fortified margarine	2 tablespoons	30	215	Tr	24	Tr	Tr	0	990	Tr	0	Tr	0
			2100	89	99	222	1461	13.2	10,670	1.58	2.79	13.6	153

* Average values for each food group have been computed according to the percentage distribution of food supplies as described in *Planning Food for Institutions*, Agriculture Handbook No. 16, U. S. Department of Agriculture, 1951, table 6.

Food values used are those published in *Composition of Foods—Raw, Processed, Prepared*, by B. K. Watt and A. L. Merrill, Agriculture Handbook No. 8, Bureau of Human Nutrition and Home Economics, Washington, 1950.

Values for cooked foods have been used when the food is normally cooked before its use.

Calories and vitamin A have been rounded off to the nearest 5 and protein, fat, and carbohydrate to the nearest whole gram.

† Vitamin A values would be reduced to 0 for meat, poultry, and fish if an average serving of liver is not included each week.

riched bread and cereals are used, and if some meat is included daily.

A Plan for the Bland Diet

The nutritive value of a basic list of foods for the bland diet is given in Table I. This list of foods is to be regarded as a minimum, and not a complete enumeration of the needs of every individual. For example, the suggested meal plan includes additional foods to complete the menu pattern and to provide calories as needed.

Suggested Meal Pattern	*Sample Menu*
Breakfast	
Fine or strained cereal	Rice Krispies
Milk for cereal and to drink	Milk
Egg—not fried	Poached egg on buttered toast
Enriched white toast	
Butter or fortified margarine	
Citrus fruit juice	Orange juice—4 ounces
Coffee with cream or milk	Coffee with hot milk
Sugar	Sugar
Midmorning	
Milk beverage	Milk—8 ounces
Noon Meal	
Cream soup, if desired	Cream of tomato soup
Meat, fish, poultry, egg, or cheese	Macaroni and cheese
Potato or substitute	
Cooked green or yellow vegetable—low-fiber or puréed	Chopped fresh spinach
Enriched white bread	Bread
Butter or fortified margarine	Butter
Cooked fruit or ripe banana	Canned peaches
Milk	Milk
Midafternoon	
Milk beverage or dessert made with milk	Baked custard Sugar cookies
Evening Meal	
Meat, fish, or poultry	Broiled liver with crisp bacon
Potato	Creamed potatoes
Cooked vegetable—low-fiber or puréed	Baked Hubbard squash
Enriched white bread	Bread
Butter or fortified margarine	Butter
Dessert	Vanilla ice cream
Citrus fruit or tomato juice	Tomato juice—8 ounces*
Milk	Hot cocoa
Bedtime	
Milk beverage	High-protein milk
Plain cake, cookies, crackers, or sandwich	Sponge cake

Foods from Which to Choose	*Foods to Avoid*
Beverages:	
Milk and milk drinks	Alcohol
Coffee, limited to 1 cup daily, diluted with milk, cream	Carbonated beverages Coffee or tea in excess
Weak tea	
Breads:	
White enriched bread	Coarse whole-grain bread
Rye bread without seeds	Graham crackers
Melba toast; Zwieback	Fresh bread or sweet rolls
Soda crackers	Salty crackers and pretzels
Cereals:	
Cornflakes, puffed rice, rice flakes	Bran Whole-grain cereals
Farina, rice, cornmeal, hominy grits	
Macaroni, spaghetti, noodles	
Strained oatmeal, pettijohns	
Cheese:	
Cottage, cream, mild cheddar	Strongly flavored cheese
Desserts:	
Plain puddings without nuts, whole fruit or spices: bread, rice, cornstarch, tapioca	Any containing whole raw fruit, fruit with seeds; spices; or nuts
Custard; Junket	Gingerbread
Plain gelatin desserts	Doughnuts
Plain ice cream, ices, sherbets	Pastries; pies; tarts
Sponge or angel cake; sugar cookies; lady fingers	
Fruit whips	
Eggs—Any way except fried	
Fats:	
Butter or fortified margarine	Salad dressings Mineral oil

* Eight ounces of tomato juice are approximately equal to 4 ounces of orange juice in ascorbic acid content.

Foods from Which to Choose	*Foods to Avoid*
Fats (cont.):	
Cream	
Vegetable oils and fats	
Fruits:	
Raw: avocado, banana, strained citrus juices	Raw, except as listed
Cooked, without skin: apple, peach, pear, apricot	Berries
	Figs
	Pineapple
Cooked, puréed: plums, prunes, cherries	
Meats—very tender or ground	
Roasted, broiled, baked, stewed, creamed—bacon, beef, chicken, fish, lamb, liver, sweetbreads, veal	Salted or smoked meats
	Prepared luncheon meats, frankfurters
	Sausage
	Fatty meat or fish
	Tough meats
Soups:	
Cream, using allowed vegetables	Meat stock
Vegetables:	
White potato—any way except fried	Strongly flavored: cabbage, cauliflower, Brussels sprouts, cucumber, onion, radishes, green pepper, turnips, dried beans and peas; corn
Tender asparagus tips, beets, carrots, peas, string beans, sweet potato, spinach, winter squash—chopped or strained, unless tender	Raw vegetables
Miscellaneous:	
Salt and sugar in moderation	Catsup; chili sauce; meat sauces; horseradish; mustard; pepper; vinegar
Nutmeg and cinnamon	Candy; fried foods; gravies; nuts; salty foods; pickles; popcorn

Variations of the Bland Diet

Slight modifications in the plan described above make it possible to use it for a variety of needs. For some patients with peptic ulcer temporary modifications might include: (1) the omission of meat, with increased use of eggs and nonfat milk solids; (2) puréeing of all fruits and vegetables; (3) milk mixed with half cream and given at frequent intervals during the day and night—usually every two hours.

In chronic ulcerative colitis it is sometimes necessary to incorporate milk in prepared dishes rather than serving it as a beverage since idiosyncracy to milk is frequent. On the other hand, meat, poultry, and fish are usually well tolerated and may be used liberally. Meat soups, meat extractives, tea, and coffee may be used as desired.

In situations where gastric secretion and motility are decreased the bland diet may be modified by restricting the amount of fat.

Shifting Adiposity

"Shakespeare's keen observant eye, which missed little, noted that in late middle age the legs lose girth whilst the abdomen gains. What is the origin or significance of this? Some say that discontinuance of stooping conditions the abdominal adiposity; others are equally convinced that the adiposity inhibits stooping. The truth may lie in between or there may be that reciprocal reinforcement which Herbert Spencer asserted is so common a feature in biological happenings. But certainly this strange shift of fatty tissue from the legs to the abdomen is a fairly regular concomitant of old age and must have some meaning.... Truly the unexplored area in the territory of the physiology and pathology of adipose tissue is greater than the explored and demands investigation."
—"A Decreasing Leg—an Increasing Belly." Leading article. *The Medical Journal of Australia* 40: 895, 1953.

Nutrition Briefs

CURRENT OBSERVATIONS OF CLINICAL INTEREST

A STRIKING elevation of erythrocyte sedimentation rate was observed during various dietary stresses in healthy young men. This was particularly seen under conditions of starvation or a protein intake of more than 12 Gm. N, and in pure carbohydrate or high fat intakes.

E. Meltzer, F. Sargent III, and K. L. Andersen. *Fed. Proc.* 13: 99, 1954.

ISONIAZID caused an excessive excretion of vitamin B_6 in as many as 40 per cent of patients. Studies on reported INH neuritis suggest that addition of vitamin B_6 prevents isoniazid neuritis.

J. P. Biehl and R. W. Vilter. *Proc. Soc. Exper. Biol. & Med.* 85: 389, 1954

DETAILED studies on a patient with anorexia nervosa demonstrated less "conversion" and virtually no "burning" of intravenously administered human albumin. This conservation of albumin by a starving person also suggests an inability rapidly to burn or convert a sudden influx of albumin.

P. H. Henneman, A. P. Forbes, and F. Albright. *Clin. Res. Proc.* 2: 79, 1954.

METABOLIC studies in normal old men indicate that dihydrotestosterone has anabolic properties but cannot be recommended as a substitute for a high protein diet.

D. M. Watkin, J. Parsons, M. Yiengst, and N. W. Shock. *Clin. Res. Proc.* 2: 86, 1954.

CRYSTALLINE vitamin B_{12} was administered intramuscularly in various amounts to 51 healthy Mexican subjects and to a comparable group of 47 American (U. S.) subjects. Whatever the amount injected, less vitamin B_{12} was excreted in the urine of the Mexicans than in that of the American group. The explanation appears to lie in the difference in the amount of dietary vitamin B_{12} consumed by the two groups: the Mexican intake of this vitamin is estimated to be some 30 per cent lower than the American.

S. C. Estrada, C. A. Lang, and B. F. Chow. *J. Lab. & Clin. Med.* 43: 406, 1954.

THE ROLE of "diencephalic regulator" is claimed for vitamin A. The vitamin is reported to exert a favorable effect on various centrally regulated mechanisms: sleep, blood pressure, reproductive function (menstruation), and cellular proliferation. These effects are more pronounced with low ("physiologic") doses of the vitamin than when larger amounts are given, and are said to be best achieved by intravenous administration of easily assimilable forms such as aqueous suspension of axerophthol palmitate.

Y. Dhotel. *Acta vitaminol.* 7: 147, 1953.

PANTOTHENIC acid excretion was not significantly modified by the daily administration of penicillin (1,000,000 units intramuscularly), aureomycin (2 Gm. orally), or chloramphenicol (2 Gm. orally) for a 15-day period. In only a few patients did a slight but progressive decrease in urinary pantothenic acid occur during antibiotic therapy, and in these cases the values did not fall below the "low normal" limit.

L. A. Scuro. *Acta vitaminol.* 7: 143, 1953.

SUBCLINICAL nutritional deficiencies may be revealed by inspection of the tongue under Wood-Light (ultraviolet) radiation. In the healthy individual, the tongue shows fluorescence, while absence or diminution of fluorescence indicates a deficiency state.

A. B. Schaffer and S. W. Sachs. *Oral Surg., Oral Med. & Oral Path.* 6: 1425, 1953.

WHEN VITAMIN B_{12} (labeled with radioactive cobalt) was administered orally to 4 patients who had had a total gastrectomy, all of the radioactivity was excreted in the stools. When gastric juice was given simultaneously, there was a decrease in cobalt excretion indicating absorption of the vitamin. Patients with a total gastrectomy do not absorb oral vitamin B_{12} and cannot depend on dietary sources for this supply.

M. E. Swendseid, J. A. Halsted, and R. L. Libby. *Proc. Soc. Exper. Biol. & Med.* 83: 226, 1953.

PANTOTHENIC acid appears to act on human blood sugar levels by influencing the β-cells of the pancreatic islets. At high altitudes, the vitamin caused a fall in blood sugar level in 9 out of 10 subjects. At lower altitudes, it caused a fall in 3 diabetics and an elevation in 7 other persons, including one with diabetes insipidus.

E. Stangl. *Intern. Ztschr. f. Vitaminforsch.* 25: 135, 1954.

RECENT ADVANCES IN EXPERIMENTAL NUTRITION

HYPERVITAMINOSIS A, induced in weanling rats by a synthetic diet containing 50 to 250 I.U. of vitamin A per Gm. body weight, caused degenerative lesions to appear in the testis, a change which was enhanced by the concurrent administration of vitamin E. Mature rats, however, were not affected by this regimen.

C. L. Maddock, J. Cohen, and S. B. Wolbach. *Arch. Path.* 56: 333, 1953.

RESPONSE to thiopental in mice deficient in protein and in various vitamins of the B-complex was investigated by means of a new technique. Thiamine-deficient mice responded in essentially normal fashion. Mice deficient in B-complex vitamins showed a moderately enhanced response. In niacin deficiency, the response to thiopental was most accentuated.

H. A. Levy, J. R. DiPalma, and C. Alper. *J. Pharmacol. & Exper. Therapy* 109: 377, 1953.

FETAL and maternal levels of pantothenic acid in the liver of rats were found to be correlated. In pregnant rats deprived of pantothenic acid, the hepatic level of this vitamin fell 40 per cent, as compared to controls; all of these deprived animals aborted. Less severe deficiency states caused fetal deformities.

A. Giroud, G. Lévy, and J. Lefebvres. *Intern. Ztschr. f. Vitaminforsch.* 25: 148, 1954.

PREGNANT rats were fed a synthetic diet without folic acid, and intestinal synthesis of folic acid was concomitantly suppressed. Under these circumstances, a reduction in hepatic pantothenic acid occurred. If a secondary deficiency of the latter substance occurs in folic acid deprivation, the occurrence of fetal malformations of the type caused by primary pantothenic acid deficiency might be explained on this basis. However, since variations in maternal pantothenic acid level were not clearly demonstrated in the fetus, this hypothesis cannot be accepted without reservation.

A. Giroud, G. Lévy, and J. Lefebvres. *Intern. Ztschr. f. Vitaminforsch.* 25: 153, 1954.

ASCORBIC acid deficiency in guinea pigs is accompanied by hypertrophy of pancreatic islet tissue and a fall in the β/α cell ratio. Changes in the β/α ration paralleled other signs of scurvy—weight loss and diminished tooth protection—but were somewhat more sensitive indicators of the degree of deficiency than these signs. It is suggested that scorbutic guinea pigs may be less sensitive to the hypoglycemic action of insulin, and that islet tissue hypertrophy may be caused by an increased need for insulin. The mechanism of this hypertrophy, with an increase in α-cells (presumably β-cell precursors) is not yet clear.

N. Allegretti. *Intern. Ztschr. f. Vitaminforsch.* 25: 125, 1954.

THIAMINE deficiency was induced by feeding adult dogs a diet of autoclaved canned dog food, plus supplements of all vitamins except thiamine. The characteristic signs of thiamine deficiency appeared, with abnormal pyruvate and lactate utilization, impaired glucose extraction by the myocardium, and abnormal oxygen utilization—expressed by the limitation placed on myocardial oxygen extraction coefficient by the higher rate of coronary flow which accompanies acute thiamine deficiency.

D. B. Hackel, W. T. Goodale, and J. Kleinerman. *Am. Heart J.* 46: 883, 1953.

IN GROWING rats on a diet lacking pantothenic acid, this vitamin can be replaced, to a variable extent, by the following antibiotics: aureomycin, penicillin, chloramphenicol, and dihydrostreptomycin. During a 5-week period, weight increases on the various regimens were: controls (standard diet), 100%; controls on diet lacking pantothenic acid, 19.98%; rats deprived of pantothenic acid receiving supplements (0.05%) of (a) aureomycin, 74.13%, (b) penicillin, 55.02%, (c) chloramphenicol, 54.60%, (d) dihydrostreptomycin, 42.05%. Furthermore, circulating antibodies which are reduced in pantothenic acid deficiency remained within normal limits in rats receiving antibiotic supplements.

G. Guinchi, A. Fidanza, L. A. Scuro, and F. Sorice. *Intern. Ztschr. f. Vitaminforsch.* 25: 1, 1953.

Nutritional Quotes

To Each His Own...Vitamins

"Primitive insect species such as *Blatella germanica* have a very complex requirement for the common water-soluble vitamins and for essential amino acids but seem to have no need for fat-soluble vitamins such as A and D. The need for these fat-soluble vitamins must have arisen with the vertebrates. Among vertebrates have arisen very diverse vitamin needs. Even various species of fish have specific requirements that resemble those of higher species. Cats, mink and trout all seem to require some thermolabile factors found in raw meat or milk. By way of contrast, dogs, rats and foxes can pass through the whole life cycle when fed heat-treated foodstuffs. In some species a specific vitamin deficiency does not appear until the arrival of the second generation. Thus dogs can grow satisfactorily from weaning to maturity upon vegetarian diets deficient in vitamin B_{12} but pups from such bitches die soon after birth or develop very poorly. Ascorbic acid provides one of the enigmas of comparative nutrition since a primitive insect such as the cockroach seems able to create it, but man, monkey and the guinea pig cannot."

—C. M. McCay in an address presented at the 3rd Science Day, Milan, April 12–16, 1953, on "The Evolution of Vitamin Needs from Insects to Man." (Abstracted in *Acta vitaminol.* 7: 59, 1953.)

Eating Habits in Alcoholism

"Most patients showing physical effects of chronic alcoholism also had evidence, direct or indirect, of inadequate nutrition. Dietary histories under these circumstances are notoriously unreliable; but the general pattern was 'no breakfast, a small lunch consisting of sandwiches, and a small dinner of meat and vegetables.'"

—J. Isbister. *The Medical Journal of Australia* I: 360, 1954.

Metabolic Roles of Ascorbic Acid

"It is clearly established that vitamin C is involved in two distinct chemical reactions, or systems, namely: (i) the conversion of folic acid to folinic acid, (ii) the metabolism of tyrosine and related substances. An additional point here, as suggested by the new findings of King (1953), is that in vitamin C deficiency cholesterol metabolism may also be affected. Apart from this, little is definite."

—L. J. Harris. *Proceedings of the Nutrition Society* 12: 273, 1953.

The Natural Nature of Obesity

"It is most remarkable that so much research and so many hypotheses have centered round the nature of obesity, as if it was a mysterious negation of the laws of nature. Perhaps obese patients have been too readily believed when they protest vehemently that they eat next to nothing. Perhaps gullible clinicians have thus tried to evoke endocrine dysfunction, fluid retention, hypothalamic disturbances, and psychological troubles as acceptable explanations. But, however we try to escape from it, we are always confronted at last with the fundamental law that matter cannot be created or destroyed. Nobody can make fat out of nothing. As Rynearson so trenchantly put it: 'Fat comes from food; where the hell else can it come from?'"

—L. Martin. *The Medical Press* 231: 409–410, 1954.

Obesity: Some Definitions

"Before considering the factors concerned with the appearance of obesity, it is essential to understand the somewhat confusing and ambiguous nomenclature of the subject. Thus *obesity* means an abnormally large body-weight due to deposition of fat. *Adiposity* means that an individual has abnormal general or local deposits of fat, but need not necessarily be over average weight. The term *overweight* is merely descriptive and means that an individual is unduly heavy, whether from fatty deposits, the presence of oedema, ascites, a pregnant uterus, or any other cause."

—L. Martin. *The Medical Press* 231: 409, 1954.

Vitamins as Drugs

"The so-called 'vitamins' enter the pharmacological field when they leave that of biochemistry, i.e., when they become chemicals extraneous to their original function, owing to the administration of different dosages, to a different way of administration, or to different influences displayed by them.... Becoming drugs, they are no longer a class and share in the usual questions relating to any drug (problems of chemical and physical constitution and of pharmacological action, questions relating to absorption, metabolism, cumulation, excretion, to a different effect according to the dose, to addiction, idiosyncrasy, to general and local effects, and even to race).

An important relation between vitamins and drugs is represented by the devitaminizing action of many common drugs."

—P. Di Mattei in an address presented at the 3rd Science Day, Milan, April 12–16, 1953, on "Vitamins in Pharmacology." (Abstracted in *Acta vitaminol.* 7: 81, 1953.)

Reviews of Recent Books

Clinical Endocrinology by K. E. Paschkis, A. E. Rakoff, and A. Cantarow, Hoeber-Harper, New York, 1954, pp. 830, $16.00.

When, among their prefatory remarks, the authors declare that endocrinology has emerged within a relatively brief period as a "highly respected and dignified member of the family of medical specialties," we must recognize that this admirable status has been achieved in part through their own efforts and contributions in this field. In the present work, one finds an integration of the biochemical, physiological, and clinical data referable to specific endocrine systems. Each gland is discussed individually from the standpoint of its development, role in cellular metabolism, and in relationship to pathologic physiology in which it may become involved. Specific diseases are found in separate chapters under the heading of hyperfunction or hypofunction of the gland in question.

In addition to the thorough coverage of the endocrinological disorders, there is a rather brief section on obesity. Here, one would like to find more exact references to dietary plans rather than general schemes for weight reduction; the highly successful group therapy methods are not mentioned. The attractive "glucostatic theory" of Mayer is not presented in this section. The final chapter of the book should prove extremely useful, as it presents the current procedures employed in the investigation of endocrine disease, together with methods and interpretations.

As might be expected, the section on the ovary is outstanding. The authors have accumulated herein a wealth of fundamental data which will aid the reader in orienting himself quite adequately in this complex area. The sections on the adrenal, thyroid, and parathyroid glands offer complete presentations of the actions of these organs in health and disease, with detailed discussions as to management of the disorders in which they are involved. Somewhat less satisfactory, however, is the section dealing with the treatment of diabetes mellitus.

Each chapter is supplied with numerous references, and a useful table of commercially available hormone preparations is found at the end of the text. This volume should provide the practitioner with an excellent foundation from which he can build a full understanding of the endocrine glands and their disorders and provide his patients with appropriate treatment based upon this knowledge.—CHARLES R. SHUMAN

Books received for review by the *Journal of Clinical Nutrition* are acknowledged in this column. As far as practicable, those of special interest are selected, as space permits, for a more extensive review.

Elements of Food Engineering. Vol. 1 by M. E. Parker, w. the collab. of E. H. Harvey and E. S. Statler, Reinhold Pub. Corp., New York, 1952, pp. 386, $8.75.

The Biochemistry of the Nucleic Acids (ed. 2) by J. N. Davidson, John Wiley & Sons, Inc., New York, 1954, pp. 200, $2.25.

The Vitamins: Chemistry, Physiology, Pathology. Vol. I, edited by W. H. Sebrell, Jr., and R. S. Harris, Academic Press Inc., New York, 1954, pp. 676, $16.50.

Symposium on Protein Metabolism, National Vitamin Foundation, Inc., New York, 1954, pp. 103, $1.50.

Newer Concepts of the Causes and Treatment of Diabetes Mellitus, National Vitamin Foundation, Inc., New York, 1954, pp. 177, $2.50.

Nutrition and Physical Fitness (ed. 6) by L. Jean Bogert, W. B. Saunders Co., Philadelphia, 1954, pp. 664, $4.50.

Wine as Food and Medicine by S. P. Lucia, The Blakiston Co., Inc., New York/Toronto, 1954, pp. 149, $3.00.

Colloque sur les acides aminés, S. Karger, Basel/New York, 1954, pp. 333, Sw. fr. 25.

Submicroscopic Morphology of Protoplasm (Eng. ed. 2) by A. Frey-Wyssling, Elsevier Press, Houston, 1953, pp. 411, $8.50.

Cell Chemistry by D. Burk, Elsevier Press, Houston, 1954, pp. 359, $7.50.

Vitamins and Hormones, edited by R. S. Harris, G. F. Marrian, and K. V. Thimann, Academic Press Inc., New York, 1953, pp. 356, $8.50.

The Year Book of Endocrinology (1953–1954), edited by G. S. Gordon, Year Book Publishers, Inc., Chicago, 1954, pp. 390, $6.00.

Energy Metabolism and Nutrition by R. W. Swift and C. E. French, The Scarecrow Press, Washington, D. C., 1954, pp. 264, $5.75.

Abstracts of Current Literature

FAT METABOLISM

(a) ACTION OF CHOLINE

Choline has a profound effect upon the fatty liver which develops in depancreatized animals. The lipotropic action of choline has been thought to involve its incorporation into phospholipid as an intact molecule. However, this hypothesis involving phospholipid formation has not been clearly established. In humans with chronic hepatitis, choline and its methylating precursor methionine were found to increase the phospholipid turnover, presumably through their lipotropic action. However, in the following study, it is suggested that the lipotropic effect of choline may be due to the enhancement of fatty acid oxidation within the liver.

Role of Choline in the Oxidation of Fatty Acids by the Liver. C. Artom. *J. Biol. Chem.* 205: 101, 1953.

The oxidation of isotopic long-chain fatty acids was depressed in liver preparations from choline-deficient animals, and choline, administered *in vivo*, restored the ability of the tissue to oxidize the labeled fatty acids at a high rate. Such results are in line with the idea that the lipotropic effect of choline is due to an increased rate of fatty acid oxidation in the liver rather than to transport out of the liver as plasma phospholipids. Liver preparations of rats maintained on various diets varying in choline and protein content were incubated with C^{14}-labeled stearate or palmitate, and the radioactivity of the CO_2 evolved during the incubation period was determined. Liver preparations from rats on the low protein diet which had been supplemented with choline had the ability to produce $C^{14}O_2$ at a higher rate than preparations from rats supplemented with guanidoacetic acid. Differences in the amounts of labeled acetoacetate formed during the incubation paralleled those in the amounts of $C^{14}O_2$. *In vitro* additions of choline, betaine aldehyde, betaine, or phosphorylcholine did not stimulate the production of $C^{14}O_2$.

These findings support the suggestion that the lipotropic effect of choline may, to a large extent, be due to the enhancement of fatty acid oxidation in the liver by some substances formed from choline *in vivo*.—M. K. HORWITT

The availability of choline apparently governs the quantity of methionine used for protein synthesis. When dietary choline is deficient larger amounts of methionine are required as methyl donors. This is probably of much greater significance for the experimental animal than for the human. The effect of choline deficiency upon the serum proteins of the rat serves to illustrate these interrelationships.

Protein Metabolism in the Choline-Deficient Rat. I. Effect of Choline on Serum Proteins. M. A. Fischer and G. C. Garrity. *J. Biol. Chem.* 204: 757, 1953.

Unless the choline content is sufficient to supply all of the required methyl groups, the amount of choline in a diet apparently determines the quantity of methionine used for protein synthesis and the quantity reserved for use as a methyl donor. In the present study, electrophoretic patterns of sera from rats fed a choline-deficient diet were compared with those from rats fed choline supplements. An 18 per

cent casein diet did not provide all of the factors essential for the maintenance of normal serum albumin concentration and the kidney damage which resulted in these severely deficient animals caused the concentrations of the α-globulins and one of the β-globulins of the sera to increase.

The basal diet used on the rats (weanlings) caused an almost immediate increase of fat in the liver, and renal lesions became evident on the sixth day. Two mg. of choline chloride per day prevented the damage to the kidneys to a large extent, but approximately 6 mg. of choline per day was necessary to prevent the formation of liver fat. The serum albumin concentrations of the choline-deficient rats did not differ from that of the choline-fed controls until kidney lesions appeared; then the albumin concentration was lower in the deficient animals than in the controls. Increases in phospholipid, α-globulin, and β-globulin were demonstrated in the sera of the deficient animals. These changes seem to be related to the degeneration of the kidney tissue. Although there was no apparent alteration in the rat serum γ-globulin content on either the basal diet or the basal diet plus choline, when choline was administered to deficient animals in order to speed their recovery, the γ-globulin concentration increased.—M. K. HORWITT

Diets low in choline and high in fatty acid content are associated with a reduction in choline oxidase activity.

Relation of Choline Oxidase Activity to Dietary Fatty Livers. F. L. Humoller, and H. J. Zimmerman. *Am. J. Physiol.* 174: 199, 1953.

When rats are fed on a diet high in fat but low in choline the liver choline-oxidase is markedly reduced. This decrease takes place abruptly during the first week. Later it becomes constant even though the diet is continued. During the three weeks of the experiment the liver fat continued to rise. Fatty acids inhibit choline-oxidase of normal and dietary fatty liver homogenates. Choline and betaine injected two hours before sacrificing rats with dietary fatty livers did not change the choline-oxidase activity of such livers. These same agents did not increase endogenous oxygen use of similar homogenates.—M. J. OPPENHEIMER

It is apparent that essential amino acids are required for normal liver metabolism, since diets adequate in choline content but deficient in certain essential amino acids are capable of producing high fat deposition in this organ.

Factors other than Choline which Affect the Deposition of Liver Fat. A. E. Harper, W. J. Monson, D. A. Benton, M. E. Winje, and C. A. Elvehjem. *J. Biol. Chem.* 206: 151, 1954.

It had previously been shown that the amount of fat which accumulates in the livers of young rats fed 9 per cent casein-sucrose diets containing choline is greatly reduced when protein or threonine is included in the diet. This study evaluated some of the factors which influence the effectiveness of additional dietary threonine in lowering fat deposition in the livers of weanling rats receiving low casein diets containing choline.

Threonine is more effective in reducing liver fat where the diet contains 10 per cent casein than when it contains less casein, and this observation was interpreted as an indication that other amino acids are implicated, although betaine, glycine, and serine were each only partially effective. Certain combinations of these were almost as effective as threonine.

Although threonine was not effective in the absence of choline, the high fat deposition observed in the livers of weanling rats receiving choline indicates that the lipotropic action of proteins cannot be explained entirely on the basis of their methionine-cystine ration. It would seem that at least three groups of normal dietary substances must be considered: (a) choline which is essential for phospholipid formation and which can be replaced by methionine, (b) threonine and probably other essential amino acids which may be required for the formation of an enzyme or enzymes necessary for normal liver metabolism, and (c) glycine, serine, betaine, and related substances which may act in a nonspecific manner by sparing essential compounds.—M. K. HORWITT

(b) OTHER ASPECTS

Endogenous fat is produced from acetate and acetoacetic acid, which may be derived from dietary carbohydrate. The fat depots derived from this source will supply the patient with a compact repository of potential energy to be utilized during periods of low caloric intake. The ability of the organism to convert these substrates into fat depends upon the nutritional state and upon the presence of normal glycolysis, for which insulin is necessary.

Acetoacetate Conversion to Fatty Acids in Liver: The Role of Insulin and the Nutritional State of the Animal. R. W. Chen, D. D. Chapman, and I. L. Chaikoff. *J. Biol. Chem.* 205: 383, 1953.

Using acetoacetic acid-3-C^{14} and ethyl acetoacetate-3-C^{14}, the incorporation of the carbonyl carbon of acetoacetate into CO_2 and long-chain fatty acids by surviving liver slices prepared from normal fed, normal fasted, fed diabetic, and insulin-treated fed diabetic rats was studied. The rats were made diabetic by a single intravenous injection of alloxan monohydrate. During the last 3 days prior to sacrifice, they were fasted or fed either a 60 per cent glucose diet or Purina laboratory chow. Some of the diabetic rats were given insulin during the 2 days before they were sacrificed. Slices from the livers of these animals were incubated for 3 hours at 38° with acetate and acetoacetate substrates to give the results which

indicate that the carbonyl carbon of acetoacetate is converted to CO_2 by the liver, and that this carbon of acetoacetate is also incorporated into fatty acids. The extent of this incorporation is dependent on the nutritional state of the rat. The incorporation was considerable in the livers of normal fed rats, but the capacity for this conversion is lost by the livers of the normal fasted and fed diabetic rat. Insulin injections into diabetic rats restored to normal the capacity of their livers to form fatty acids from acetoacetate. These data are significant, since ketosis develops in fasting and in diabetes, and it is in these two conditions that the loss in the capacity of the liver to incorporate acetate as well as acetoacetate carbon into fatty acid has been observed. Although the rate of fat oxidation is probably the most important factor in the development of ketosis, the results presented suggest that depressed utilization of acetoacetic acid in liver also plays a part in ketone body accumulation in diabetes and in fasting.—M. K. Horwitt

The focal point for the utilization of fats is probably the liver, in which the oxidation of fatty acids disrupts the molecule into 2-carbon fragments so that, in combination with coenzyme A, these substances can be metabolized by most tissues. Fat is brought to the liver from the fat depots by way of the bloodstream. The rate of this mobilization is controlled by multiple factors, the nature of which is not clearly understood.

The Liver and Fat Transport. C. D. Langen. *Gastroenterologia* 80: 1, 1953.

In this stimulating discussion of some of the more mysterious operations of the liver, the author poses the question of the role of this organ in fat transport and offers experimental evidence suggesting the answer.

The level of lipemia gives us information only on fat *en route*, not on its origin or destination. These blood-borne lipids may be headed from the liver to the periphery, or newly arrived from the intestine, or perhaps they have left their depots and are on their way to the liver to be prepared for future missions.

Sinclair has demonstrated that liver lipids are largely incorporated into phospholipids of two different types, one concerned with metabolism, the other with structure. The liver releases these phospholipids, while depot fat is forwarded to the liver in the form of neutral fat and is there adapted to its ultimate role. Blood lipid level reflects the sum of all these multidirectional peregrinations of the lipids.

In clinical and experimental hyperlipemia, we are dealing with lipids derived from depots and accumulating in the liver. Similarly, hyperlipemia (caused principally by increased neutral fat) is seen in absolute fasting—if the nutritional state is good and depots are not largely exhausted. Also, during heavy exercise, neutral fat transport to the liver is increased, a process which can be accentuated by fasting or by withholding fats and carbohydrates and checked by simultaneous administration of carbohydrates.

In experimentally anemic animals, the serum lipid level is sharply increased when the erythrocytes fall to about 2,000,000 and falls rapidly when the count rises to 2,500,000 per mm.^{3} The author suggests that this mobilization of depot fat represents a response to an "alarm state," and that the rapid shifts in serum lipids are produced by some *central regulation*. If the spinal cord of one of these animals is cut at the level of the fourth and fifth thoracic vertebrae (or if all nerve fibers leaving the cord at the fourth thoracic vertebra are cut), *hyperlipemia no longer appears* when the critical limit of 2 million erythrocytes is reached. If the cord or nerves are severed at the level of the eighth thoracic segment or below, hyperlipemia occurs as usual.

Further illumination of these mechanisms is afforded by a consideration of the very different effects of various narcotics on serum lipid levels. Barbiturates provoke hyperlipemia; the site of action is the mesencephalon and the many vegetative nervous centers it controls. On the other hand, other narcotics whose action is on higher centers and in the cortex do not affect serum lipid levels.

The author deduces that there must exist in the diencephalon a *lipid regulation center* which determines fat mobilization and transport to the liver. This center may inhibit fat mobilization; another factor may stimulate it. This would explain why narcosis of the vegetative center by barbituric acid would leave the stimulating factor uncontrolled, with resulting hyperlipemia. Tentatively, then, the author suggests that the mesencephalon controls impulses which regulate mobilization of depot fats, but that this influence is not exerted directly on depot fats but indirectly, particularly by way of the liver. Hence, the liver would seem to regulate not only phospholipid transport to the periphery, but also the movement of depot lipids to itself. *How* the liver exercises this control, and what nervous pathways and possible hormonal factors are involved, is still an open question.—C.-J. Howell

In connection with the mobilization of fat, certain hormonal factors have been studied, including growth hormone, the adrenal steroids, and, in the following paper, epinephrine.

Role of Neurohumors in the Action of the Adrenal Cortical Steroids: Mobilization of Fat. I. G. Wool, and M. S. Goldstein. *Am. J. Physiol.* 175: 303, 1953.

When ethionine is administered to fasted female rats fatty livers are produced. Adrenalectomy prevents this effect. This is not restored by cortisone nor by epinephrine alone. When these hormones were used together, fatty livers appeared as in control animals. The authors are of the opinion that the inability of adrenalectomized animals to mobilize fats

depends on an altered sensitivity to epinephrine.—M. J. OPPENHEIMER

Another hormone which may be of significance in fat metabolism is the hyperglycemic-glycogenolytic factor. In association with its effect in raising the blood sugar, it has been shown to inhibit the synthesis of fatty acids from acetate.

The Effect of Hyperglycemic-Glycogenolytic Factor on Fat Metabolism of Liver. E. S. Haugaard and N. Haugaard. *J. Biol. Chem.* 206: 641, 1954.

This paper reports experiments on the synthesis of fatty acids from isotopic glucose and fructose and on the formation of ketone bodies by rat liver slices. Using male albino rats of the Wistar strain, studies of the effect of the hyperglycemic-glycogenolytic factor (HGF) (Glucagon) on the synthesis of fatty acids by liver slices showed that the addition of HGF caused an average decrease of the fatty acid synthesis of about 30 per cent. This value is similar to the inhibition which these authors have previously reported by the HGF factor on the incorporation of acetate into fatty acids. HGF increased the formation of ketone bodies by rat liver slices, both in the absence of substrate and in the presence of acetate.

The overall effect of HGF to permit oxidation of fatty acids and to inhibit synthesis is the opposite of that of insulin. In general, the experiments give further evidence that the hyperglycemic-glycogenolytic factor influences metabolic reactions and adds support to the view that it plays a role in the regulation of metabolism in the intact animal.—M. K. HORWITT

It is interesting that high protein diets, which have been shown to be capable of preventing fatty infiltration of the liver, are also capable of decreasing the fecal fat content.

Effect of Dietary Protein on the Fat Content of Feces. D. F. Magee, K. S. Kim, and A. C. Ivy. *Am. J. Physiol.* 175: 310, 1953.

When casein was substituted for an equal amount of carbohydrate in a synthetic diet fed to dogs there was a decrease in fecal fat. This was true even though the diet contained as much as 27 per cent fat. High carbohydrate diets produced a higher fecal fat than isocaloric high protein diets. The possibility is noted that added casein has a cholepoietic effect. An increase in pancreatic lipase due to high protein diet may also be a factor.—M. J. OPPENHEIMER

The physicochemical properties of the circulating lipids have been extensively studied by numerous investigators. These studies are of particular interest to those concerned with the problem of the pathogenesis of arteriosclerosis. The following papers deal with various aspects of this problem.

Fatty Acid Absorption and Chylomicrons. H. Singer, J. Sporn, and H. Necheles. *Science* 118: 723, 1953.

The authors studied oleic acid absorption in intact and Thiry fistula dogs. When oleic acid was added to the Thiry loop, chylomicronemia began one hour after administration and continued for four hours. The chylomicronemia after oral administration was of somewhat greater magnitude than in the previous experiment. The addition of bile salt gave rise to a greater degree of chylomicronemia, especially when compared with the absorption of oleic acid from the fistula in the absence of bile.

The authors conclude that oleic acid is absorbed through the lymphatics. Bile salts may not be necessary for long-chain fatty acid absorption but may enhance it.—S. O. WAIFE

Role of Serum Albumin in Lipemia Clearing Reaction. R. S. Gordon, Jr., E. Boyle, R. K. Brown, A. Cherkes, and C. B. Anfinsen. *Proc. Soc. Exper. Biol. & Med.* 84: 168, 1953.

Intravenous administration of heparin results in "clearing" of lipemia. This effect requires a co-factor; this is protein in nature. Fractionation procedures, designed to identify this protein factor, indicated that it was closely allied to or identical with the serum albumin. Addition of sodium oleate inhibits the effect of albumin. Sodium palmitate acts similarly, but glycerol has no demonstrable effect. It has been found that during the clearing reaction, fats are hydrolyzed to liberate the fatty acids; that fatty acids can inhibit the clearing reaction as shown by these experiments. The authors, therefore, believe that serum albumin acts by binding and thereby removing the fatty acids evolved. The addition of whole normal serum in minute amounts enhances the effect of the albumin, indicating a second co-factor. This has not been identified.—L. W. KINSELL

Venoarterial Lipid Difference and Hyperlipemia. N. Törnblom. *Acta med. scandinav.* 146: 224, 1953.

Quite by accident the author discovered that the total serum lipids were different in the arterial and venous blood of a patient with hyperlipemia. A study was then made of the venoarterial lipid difference in 35 obese patients whose weight ranged from at least 22 to 130 per cent above the ideal weight.

In two patients the fasting blood glucose level was elevated; and just over half of the remainder had a diabetic oral glucose tolerance curve. Blood samples were drawn about noon, with the patients (as well as nine healthy students as controls), fasting. It was found that the lipid content of venous serum almost invariably exceeded that of arterial serum. Furthermore, subjects whose venous serum was rich in lipids, as a rule, had a large venoarterial lipid difference. A close coefficient of correlation was found between this arteriovenous lipid difference and the lipid con-

tent of the venous serum. This finding offers certain items for speculation and perhaps should be investigated further.—S. O. WAIFE

Earlier work suggested that the administration of the so-called lipotropic substances, methionine and choline, was capable of favorably influencing the serum lipid concentrations, ratios, and lipoprotein spectra. More recently, work has been reported which would cast some doubt upon earlier enthusiasm.

An Evaluation of the Influence of DL-Methionine Treatment on the Serum Lipids of Adult American Males. G. V. Mann, D. L. Farnsworth, and F. J. Stare. *New England J. Med.* 249: 1018, 1953.

Twenty-four men with a lipoprotein level of the S_f 12–20 class of 50 mg. per 100 cc. or more were given, in addition to their usual diet, 3 Gm. of methionine daily for 42 days. No significant change was noted in the lipoprotein level during the experimental period, indicating the methionine supplements had no effect on this group of serum lipids.—M. W. BATES

Failure of Choline Therapy to Alter Serum Lipids in Patients with Coronary Artery Disease. S. U. Greenberg and M. Bruger. *Proc. Soc. Exper. Biol. & Med.* 84: 87, 1953.

The oral administration of four and one-half grams of choline daily for 1.5 to 8.0 months to 11 patients with coronary insufficiency or myocardial infarction or both failed to alter the total serum cholesterol, the serum phospholipid, or the ratio between the two.—L. W. KINSELL

The following widely quoted paper presents data suggesting that the increased usage of fat in the daily diet is an etiologic factor in the increased incidence of atherosclerosis. It may be of interest to attempt a correlation between the incidence of atherosclerosis and the amount of physical activity required in the daily lives of large segments of the population in various parts of the world.

Prediction and Possible Prevention of Coronary Disease. A. Keys. *Am. J. Pub. Health* 43: 1399, 1953.

A correlation between fat content of the diet and the incidence of coronary heart disease is suggested, which is supported by substantial statistical data. Since cholesterol is the main substance deposited in coronary artery lesions, it seems reasonable to measure levels of blood serum cholesterol in any study of atherosclerosis. When this was done in a group of Minneapolis subjects, a direct correlation was found between changes in amount of total fat in the diet and changes in the blood serum cholesterol level. The addition or removal of cholesterol from the diet did not change the results.

The significance of this observation is enhanced by the following facts: The fat content of the average American diet has increased in the last forty years from 30 to 40 per cent of the total calories. No other country has as high a fat consumption. Serum cholesterol levels of clinically healthy men in the United States were compared to cholesterol levels of healthy men from Naples, London, and Madrid. The per cent of calories obtained from fat in the diet and the serum cholesterol values were correlated. The higher the level of fat consumption, the higher the level of serum cholesterol, especially after the age of fifty. There was no correlation between relative incidence of obesity of the populations being compared and serum cholesterol levels.

The correlation between serum cholesterol values and the dietary fat level is reflected in the incidence and mortality from coronary and related heart disease. For men aged 40–44 and 50–54 years, the United States has the highest death rate ascribed to all circulatory diseases and degenerative heart disease, which is predominantly coronary heart disease.

Next, the total death rate in various countries was compared from all causes, retaining age and sex specifications. The mortality in the United States of males aged from 40 to 65 years is surprisingly high, surpassed only by two other countries, Japan and Portugal, even though the death rates due to other diseases, e.g., neoplasms, hepatic cirrhosis, nephritis, and nephrosis, are similar. The high mortality can be explained by the increased incidence of coronary disease.

The data presented in this article seem to incriminate the increased usage of fat in the daily diet as an etiologic factor in the increased incidence of atherosclerosis in the United States.—M. W. BATES

AMINO ACIDS AND PROTEIN METABOLISM

The metabolism of protein involves the absorption of amino acids into the portal system following the digestion of protein. In the liver, the amino acids enter the "pool" of the body. The synthesis of new protein depends upon the availability of energy, intact biosynthetic mechanisms of an enzymic nature, and proper concentrations of essential amino acids. By means of cannulation of the portal vein of dogs it has been possible to study the concentration of amino acids absorbed following the feeding of certain proteins.

Availability of Amino Acids in Vivo. A. E. Denton and C. A. Elvehjem. *J. Biol. Chem.* 206: 449, 1954.

Having successfully cannulated the portal vein of dogs, studies were begun to determine whether there was a difference in the time and extent of absorption of amino acids after feeding different proteins. Dogs were maintained on a complete semipurified ration

which provided approximately 19 per cent protein. Using casein, zein, and ground beef as the sources of protein, the concentrations of amino acids in blood plasma, obtained from the portal vein and from the radial vein, were determined at 0, 1, $2^1/_2$, and 5 hours after feeding, respectively. There is a marked difference between the amino acid concentrations in the blood plasma following the ingestion of beef and zein. The peak of absorption for the amino acids after feeding beef appears to be at $2^1/_2$ hours, but there is no significant increase in the concentration of amino acids in the blood plasma from the portal vein until 4 hours after feeding.

Concentrations of amino acids in the portal vein increased soon after the feeding of casein or beef, the increases appearing to be proportional to the amounts of amino acid supplied by the protein. This indicates that the amino acids from these two proteins are similarly available. After feeding zein, the concentrations of amino acids in the blood from the portal vein decreased before showing an increase. It seems possible that the carbohydrate moiety of the ration containing zein as a source of protein may be absorbed before the amino acids, thereby causing a decrease in amino acid concentrations.—M. K. Horwitt

Amino Acid Concentration in the Portal Vein after Ingestion of Amino Acid. A. E. Denton and C. A. Elvehjem. *J. Biol. Chem.* 206: 455, 1954.

A report is presented of experiments conducted to determine the rate and extent of absorption of amino acids from the intestinal tract when fed with a complete ration to dogs. The effects of feeding a nonprotein ration on the amino acid composition of the blood plasma from the portal vein were also studied. The portal vein of dogs was cannulated as previously reported and samples of blood from the portal vein were obtained at various intervals after feeding the experimental rations. When amino acids were used as a source of protein on two different dogs it was noted that there was an immediate (0.5 hour) increase in the concentration of amino acids in the portal vein following ingestion. In both experiments there were two concentration maxima, one at 1 hour and one at 2.5 hours after feeding the amino acid ration. The concentrations of most of the amino acids increased again at 6 hours. There seemed to be a rapid absorption of all amino acids, with the exception of phenylalanine and possibly leucine. When a nonprotein ration in which sucrose was substituted for the amino acid was fed to the dogs, there was a decrease of the concentrations of all amino acids except tryptophane in the blood plasma from the portal vein.—M. K. Horwitt

Using human volunteers, Dr. Rose has established amino acid requirements by means of nitrogen balance techniques. The essential amino acids in human nutrition are tabulated below.

The Amino Acid Requirements of Man. V. The Role of Lysine, Arginine and Tryptophan. W. C. Rose, W. J. Haines, and D. T. Warner. *J. Biol. Chem.* 206: 421, 1954.

This paper continues the classical series in which the amino acid requirements are evaluated by means of the nitrogen balance techniques, using student volunteers in Dr. Rose's laboratory. In brief, the technique consists of the ingestion of an artificial diet composed of mixtures of highly purified amino acids with appropriate amounts of starch, sucrose, butter fat, inorganic salts, and vitamins. The amino acid under investigation is omitted from the artificial mixture, and the effects on nitrogen retention are determined. In 2 subjects, who subsisted on the diet deficient in lysine, a negative nitrogen balance of approximately 1.8 Gm. nitrogen per day was obtained after 4 days on the depleted diet. Both men complained of a pronounced loss of appetite, fatigue, and nervousness; these symptoms were promptly alleviated with the return of lysine to the diet. A positive nitrogen balance was re-established on the second day. Similar experiments performed with arginine and tryptophane as the variables showed no change in nitrogen balance when arginine was removed from the diet, but a most pronounced change was obtained when tryptophane was missing. Here again, as in previous studies of amino acid deficiency, there was the pronounced loss of appetite, fatigue, etc., when the subject went into negative nitrogen balance.

The authors present a table which they entitle "The final classification of amino acids with respect to their dietary role in the maintenance of nitrogen equilibrium in normal adult man." As essential they list valine, leucine, isoleucine, threonine, methionine, phenylalanine, lysine and tryptophane. As nonessential, they list glycine, alanine, serine, cystine, tyrosine, aspartic acid, glutamic acid, proline, hydroxyproline, histidine, citrulline and arginine. This classification differs from that previously reported for the growing rat only with respect to histidine and agrinine. That histidine should prove nonessential for man was considered surprising.—M. K. Horwitt

The level of amino acids in the blood depends upon the rate of utilization for protein synthesis and the rate of deamination resulting in urea formation. In the following paper, the influence of several of the endocrine glands upon amino acid concentration in the blood is discussed.

On the Endocrine Regulation of Blood Amino Acid Content. J. M. Luck, A. C. Griffin, G. Boer, and M. Wilson. *J. Biol. Chem.* 206: 767, 1954.

This is an attempt to determine whether the amino acid lowering which has been consistently observed with epinephrine in intact animals is the result of pituitary stimulation. Whereas subcutaneously injected epinephrine markedly lowers the concentra-

tion of amino acids in the blood of normal animals, *l*-norepinephrine is without effect in intact rats but, like epinephrine, induces hypoaminoacidemia in the hypophysectomized animals. If epinephrine worked through pituitary stimulation, then it would be expected that in the hypophysectomized rat, ACTH would give a positive result in both hypophysectomized and intact animals. Cortisone, desoxycorticosterone, and testosterone were without effect, but several adrenocorticotropin preparations that were studied did lower the blood amino acid levels. This was discussed in reference to the problem of ACTH purity. Growth hormone induced hypoaminoacidemia in both intact and hypophysectomized rats. No lowering was observed, however, when this hormone was administered to adrenalectomized rats. Diethylstilbestrol induced hypoaminoacidemia in the hypophysectomized animals but not in the intact animal.

Whether or not epinephrine itself is the final effector substance inducing hypoaminoacidemia remains a provocative question.—M. K. HORWITT

Further data on the excretion of amino acids in humans indicate a remarkable degree of consistency in the excretion values in subjects consuming unrestricted diets.

Urinary Excretion of Amino Acids by Human Subjects on Unrestricted Diets. J. A. Ulrich. *Proc. Staff Meet., Mayo Clin.* 29: 210, 1954.

To establish the normal patterns of amino acid excretion in subjects on unrestricted diets, a study was made of 14 women, age 20 to 40 years, and 12 men, age 20 to 60 years. Using microbiological methods, the apparent free and total values for 14 amino acids excreted in 24 hours were determined. The excretion of free and total aspartic acid, histidine, leucine, methionine, phenylalanine, tryptophane, valine, and total threonine were significantly higher for men than for women. Only the excretion of total proline appears to be higher in females than in males. One apparently normal subject had an unusual lysine metabolism.

An interesting observation was the degree of consistency in the excretion values, even though no method of controlling or checking the diets was employed. The total amino acids excreted remained relatively constant and were not related to the urine volume.—S. O. WAIFE

The Relation of Dietary Protein Consumption to N-15 Excretion in Normal Subjects and in Cushing's Syndrome Utilizing N-15 Glycerine Orally and Intravenously. K. R. Crispell, W. Parson, and G. Harden. *J. Clin. Investigation* 33: 342, 1954.

Glycerine labeled with N^{15} was administered to normal subjects orally or intravenously and the amount excreted over a 24-hour period was studied. An increased level of protein intake caused an increased excretion of N^{15} in the urine. Similarly, a decreased protein intake was associated with a decreased excretion of the labeled nitrogen. This pattern was similar whether the labeled glycine was given orally or intravenously. It is interesting that the excretion of the labeled nitrogen was not influenced by the food ingested concurrently with glycine or ingested four hours later.

A patient with Cushing's syndrome was put on a high protein diet but this increase in protein intake did not result in an increase in the urinary excretion of N^{15} such as would be expected in normal individuals. This suggests that in Cushing's syndrome the degradation of ingested amino acids was already at a maximum and could not be further increased by increasing the dietary protein. Previous studies by these authors showed that more N^{15} was excreted by a patient with Cushing's syndrome in 24 hours than by a normal subject. Such data suggest that this represents decreased protein synthesis and increased degradation and excretion of amino acids. The earlier findings are confirmed by this study.

The explanation for the increase in the amount of N^{15} in the urine of a patient on a high protein diet would appear to be an increase in the rate of conversion of amino acids in the total amino acid pool to urea. The decrease in N^{15} in the urine of a patient on a low protein diet can be explained by a decrease in this reaction or, on the other hand, by an increase in the rate of conversion of the amino acid to tissue protein.—S. O. WAIFE

Among the group of co-factors necessary for protein synthesis, magnesium has been found to be an important member.

Influence of Protein Intake on Magnesium Requirement During Protein Synthesis. W. Menaker. *Proc. Soc. Exper. Biol. & Med.* 85: 149, 1954.

Studies on protein-depleted, magnesium-depleted animals indicate that the amount of magnesium is a limiting factor in protein synthesis. Magnesium requirement for protein metabolism increases during protein synthesis, as protein intake is increased from 7 to 14 per cent. The authors believe that their data indicate that the increased magnesium requirement is not merely for structural inclusion of magnesium in new tissue.—L. W. KINSELL

The relationship between protein metabolism and the effects of choline deficiency has been discussed in the following paper.

Protein Metabolism in the Choline-Deficient Rat. II. Effect of Age and Sex on Serum Proteins. M. A. Fischer and G. C. Garrity. *J. Biol. Chem.* 206: 345, 1954.

Because renal damage due to choline deficiency has been demonstrated only in rats which were younger than 33 days, it has been suggested that the choline

requirement of older rats is less than that of weanling animals. It has also been shown that kidney hemorrhages appeared later and were less severe in young female rats than in males of the same age and weight. This paper investigates the effects of the diet on protein metabolism in rats of both sexes and of different ages in the choline-deficient rat.

In choline-deficient rats (Sherman strain) of both sexes, increased albumin synthesis precipitates choline depletion. Kidney damage becomes acute one day earlier in the male than in the female. Increased albumin concentration was found in the sera of normal males when they were 26–30 days old. At this age or younger, the use of amino acids for albumin synthesis takes precedence over their use for choline synthesis. When the deficiency becomes severe, the areas of α_1-, α_2-, and β_1-globulin (determined electrophoretically) double in value. Older animals, beyond the time of increased albumin production, show only the signs of a borderline deficiency.

(The requirements of different growth rates of the male and female rats were not discussed by the authors in this paper.)—M. K. HORWITT

In response to a severe stress, such as burns, various metabolic changes are observed, particularly with reference to protein. It is interesting to note that various tissues will react quite differently in response to such a stress.

Incorporation of N^{15} Into Protein and P^{32} Into Nucleic Acid of the Thermally Injured Rat. J. S. Roth. *Am. J. Physiol.* 176: 417, 1954.

Urinary nitrogen increases 25 per cent after moderate burns. An increased urea production explains the rise. Incorporation of N^{15} into urea by burned rats was depressed at first, but later much increased. Ammonia excretion and incorporation of N^{15} into ammonia in burned rats were decreased. The liver, spleen, and intestine incorporated more, but kidney incorporated less N^{15} into protein in burned rats. In the same animals, turnover of protein was less than controls in liver and kidney but more in spleen and intestine. Incorporation of P^{32} into total tissue nucleic acid was reduced in the liver and intestine but was increased in the kidney and spleen of burned rats. The same direction of findings held true for P^{32} turnover, except in the kidney. There are apparently many variations of tissue responses to the stress of burning. Changes in catabolism and anabolism of protein are not always parallel to those of nucleic acid.—M. J. OPPENHEIMER

The rate of production of cholic acid by the liver can be influenced by the level of amino acid feeding.

Effect of Essential Amino Acids on Cholic Acid Production in Dogs. D. F. Magee. *Am. J. Physiol.* 176: 223, 1954.

In bile fistula dogs the *d*-essential amino acids do not increase cholic acid production. Furthermore glycine and alanine do not increase cholic acid production. On the other hand, the *l*-essential amino acids increase cholic acid as the logarithm of the molar amount added. The positive effect of casein depends on the millimoles of essential amino acids which it contains.—M. J. OPPENHEIMER

VITAMIN A

Large doses of vitamin A have been shown to inhibit the rate of carotenization of the skin. It has been suggested that this action is derived from its interference with sulfhydryl metabolism. The mechanism of vitamin A action in this respect may be related to its unsaturated structure.

Studies on the Mode of Action of Vitamin A. P. Flesch. *J. Investig. Dermatology* 21: 421, 1953.

In order to investigate further the mechanism of the "antikeratinizing" action of large doses of vitamin A, Flesch has studied the *in vivo* and *in vitro* effects of several esters of this compound, as well as those of hydroxenin and oxenin, two of the synthetic precursors.

It has been previously suggested that vitamin A has a direct, local, and probably nonspecific effect on the epidermal cells, causing interference with sulfhydryl metabolism because of its unsaturated structure.

This report demonstrates in carefully controlled experiments that either oral or local administration of unsaturated depilatory compounds (oleic acid or vitamin A) acts directly on the hair follicles, provided the dose is large enough. It is postulated that when given orally, these compounds or their degradation products saturate the organism and are at least partly excreted through the sebaceous glands into the hair follicles and onto the skin surface.

In vitro studies show that the methyl, phenyl and palmitic esters of vitamin A inhibit tissue sulfhydryl and succinic dehydrogenase. This is apparently a common property of various vitamin A derivatives. While the concentrations of vitamin A preparations needed to demonstrate this effect are very large, it must be remembered that the amounts used clinically are equally unphysiologic, surpassing normal requirements 20 to 100 times.

The fact that the synthetic vitamin A precursor hydroxenin acts like vitamin A on keratinization, although having no other demonstrable vitamin effect, is a further point in favor of the nonspecific pharmacologic effect of vitamin A suggested by the author.

In clinical studies of two patients with ichthyosis, local improvement appeared with hydroxenin, while oxenin, another precursor, had no effect. This latter is probably due to the unstable nature of oxenin.

The active principle interfering with the sulfhydryl metabolism of the epidermis is probably an as yet

unidentified intermediary metabolic degradation product of vitamin A.—F. URBACH

Among the various circumstances associated with an increased vitamin A concentration in the blood is that of strenuous physical activity. The level of vitamin A after exertion in several instances was correlated with the physical condition of the subject, as reported below.

Effect of Strenuous Physical Activity on Blood Vitamin A and Carotene in Young Men. W. H. James and I. M. ElGindi. *Science* 118: 629, 1953.

Vitamin A and carotene analyses were made on samples of finger blood collected from normal young men before and after a 40- to 50-minute period of strenuous physical activity by members of a college track team. The average blood vitamin A level of the group increased 43 per cent during the workout, with individual variations from an increase of 106 per cent to a decrease of 22 per cent. The average carotene level decreased 10 per cent, with variations from +17 to −50 per cent. One subject, whose vitamin A level increased 106 per cent, was said to be in poor physical condition, while another, the only one to show a decrease in blood vitamin A, was in excellent shape. Further investigations are being carried out regarding this interesting finding.—S. O WAIFE

Biological assays on distillates from lard indicate that this substance contains vitamin A, which may explain the "sparing" action of lard on the utilization of vitamin A in diets.

Nature of the "Vitamin A-like Factor" in Lard. S. F. Herb, R. W. Riemenschneider, H. Kaunitz, and C. A. Slanetz. *J. Nutrition* 51: 393, 1953.

It has been previously shown that the occurrence of vitamin A deficiency in rats can be prevented by feeding them a diet containing a molecularly distilled forerun fraction from lard. In this study biological assays on molecular distillates from lard showed that lard contains vitamin A activity equivalent to about four-tenths to two units per gram. Chromatographic fractionation of unsaponifiables from lard and molecular distillates from lard yielded eluates which gave positive Carr-Price tests and typical vitamin A spectral curves, except in fractions having an extremely high ratio of unsaponifiables to units of vitamin A. The authors concluded that the biological activity of lard is largely attributable to the presence of typical vitamin A. The so-called "sparing" action of lard on utilization of added vitamin A in diets is in all probability due to the presence in lard of hitherto unrecognized typical vitamin A.—B. SURE

The following is a preliminary report on the accumulation of certain unidentified metabolites in the liver appearing during vitamin A deficiency states in animals.

Aspects of Vitamin A Deficiency in Rats. J. S. Lowe, R. A. Morton, and R. G. Harrison. *Nature* 172: 716, 1953.

The discovery that certain metabolites accumulate in tissues in the presence of deficiencies of the water-soluble vitamins stimulated a great deal of work and helped elucidate the way in which these vitamins fitted into the metabolism of carbohydrates. For many years, work in the field of vitamin A has been confined to the solution of the structure and synthesis of the vitamin and investigation of the defective low intensity vision which accompanies vitamin A deficiency states. The paper reports the discovery of the accumulation of hitherto unknown metabolites in the liver during the terminal stages of vitamin A deficiency. The exact structure of these metabolites, identified by their absorption spectrum, is not known. Data to support the working hypothesis that the new compounds are the result of dehydrogenation of cholesterol or steroid hormones are presented.—H. L. TAYLOR

Research is being conducted in order to improve the utilization of carotene in the formation of vitamin A among Chinese people.

Some Factors in the Chinese Diet Affecting Carotene Utilization. TE-CH'IN Chou, and A. L. Marlatt. *J. Nutrition* 51: 305, 1953.

Symptoms of vitamin A deficiency commonly observed among Chinese people result from limited vitamin A intakes supplied primarily by carotene from vegetables which are less well utilized than preformed vitamin A from animal sources. Therefore, methods of improving the utilization, as well as increasing the amount of carotene in the Chinese diet, stimulated this investigation. Carotene utilization has been increased by substances, such as tocopherols, lecithin, and ascorbic acid, which protect carotene from oxidation.

Liver storage of vitamin A after 4 weeks' supplementation to previously depleted rats was used to judge the effects on the biological value of carotene produced by varying the type of oil in a purified diet, by supplementing soybean oil with lecithin or ascorbic acid, and by using different vegetables as the source of carotene in a Chinese diet. Among the three oils commonly used in China, sesame oil in the diet produced significantly higher carotene utilization than did soybean oil or peanut oil. The addition of 1 per cent lecithin or 1 per cent ascorbic acid to the diet containing 5 per cent soybean oil produced no significant synergistic effects when the average daily carotene intake was 91 mg. With respect to the utilization values of carotene in vegetables readily available in China: carrots, sweet potato, and a green leafy vegetable, "woo-chei-pei," showed a relative carotene utilization of 0.56, 0.50, and 0.35, respectively, with crystalline carotene taken as 1.0, and 0.67 in the combination of these three vegetables.—B. SURE

PANTOTHENIC ACID

The brilliant work of Lipmann has paved the way for our understanding of the metabolism of the two-carbon groups through the agency of coenzyme A, of which pantothenic acid is the prosthetic group. Pantothenate deficiency may reduce the rate of utilization of acetate so that cholesterogenesis is impaired. Because of the relationship between cholesterol and the formation of steroid hormones, the importance of pantothenic acid can readily be appreciated.

The Metabolism and Function of Pantothenic Acid. D. E. Hughes. *Proc. Nutr. Soc.* 12: 83, 1953.

This review of the role of pantothenic acid in metabolic processes was delivered at a symposium in Sheffield, with Professor H. A. Krebs as chairman. The author reviews the evidence which now shows clearly that coenzyme A, which contains pantothenic acid, is the only functional form of the vitamin. In chemical terms, the function of CoA, as it is commonly abbreviated, is to catalyze the transfer of acetyl groups; thus, acetyl CoA plus choline forms acetylcholine; again, stearate with the help of CoA participates in phospholipid synthesis, etc. The liver is probably the main store of CoA, and administration of the vitamin promptly restores the enzymatic activity in deficient animals.

Early in pantothenic acid deficiency in animals, there are changes in the morphology and function of the adrenals. The cortex degenerates and may become necrotic. The relation of the vitamin to the adrenal may be described as follows: "Firstly, pantothenic acid deficiency, in common with riboflavin deficiency, would appear to stimulate the function of the adrenal cortex and the animal responds as if to a stress state. Secondly, the increased activity of the adrenal cortex involves sterol synthesis which is probably dependent on CoA. Increased demand for CoA thus occurs at a time of decreased availability and leads to the complete degeneration of the cortex." —S. O. Waife

Renal Clearance of Pantothenic Acid in Man: Inhibition by Probenecid ("Benemid"). W. P. Boger, G. M. Bayne, J. Gylfe, and L. D. Wright. *Proc. Soc. Exper. Biol. & Med.* 82: 604, 1953.

Using a microbiological method to measure the pantothenic acid content of plasma and urine, it was found that at a plasma level of 30 to 50 μg. per cc. there is significant renal tubular secretion of pantothenic acid. There is evidence that this tubular secretion is based on the same transport mechanism involved in the transport of penicillin, PSP, and para-aminohippuric acid. These authors found that probenecid inhibits the renal tubular secretion of pantothenic acid in man and thereby enhances the plasma levels which were obtained by the intravenous administration of large doses of sodium pantothenate. —S. O. Waife

Adrenal Function in Pantothenic Acid Deficiency. W. F. Perry, W. W. Hawkins, and G. R. Cumming. *Am. J. Physiol.* 172: 259, 1953.

Ninety days of pantothenic acid deficiency in rats produced a decrease in adrenal cholesterol concentration. However, the activity of adrenal succinic dehydrogenase increased for 50 days and later declined. There was no change in adrenal ascorbic acid concentration nor any loss in the ability to react to stress, using discharge of ascorbic acid as a criterion. It should be emphasized that these results were obtained only with a deficiency of pantothenic acid. Other B-complex factors were not deficient.—M. J. Oppenheimer

Pantothenic Acid Deficiency in Experimental Renal Hypertension in Dogs. L. A. Lewis and I. H. Page. *Am. J. Physiol.* 173: 359, 1953.

A pantothenic-deficient diet reduced blood pressure of hypertensive dogs to normal, but they showed weakness, anorexia, diarrhea and skin lesions which were not corrected by adrenal extract or glucose and saline injections. The condition was reversed by pantothenic acid and blood pressure rose to hypertensive levels. An agent cytotoxic for the adrenal cortex produced a moderate reduction of pressure only after intoxication. High gamma globulin in renal hypertensive dogs was decreased by pantothenic deficiency. Alpha and beta globulins were not influenced consistently. Caloric restriction and weight loss did not lower pressure.—M. J. Oppenheimer

Adrenal Function in Pantothenic Acid Deficient Rats. L. S. Hurley and F. E. D'Amour. *Fed. Proc.* 13: 74, 1954.

Rats deficient in pantothenic acid are unable to increase blood sugar levels or liver glycogen when subjected to low oxygen tensions (anoxia). In this study, normal rats exhibited a twenty-fold increase in liver glycogen under the same stress conditions. However, the cholesterol content of the adrenal glands fell in both control and pantothenate-deficient animals. The authors believe that the level of adrenal cholesterol, frequently used as an index of adrenal activation, may not be invariably reliable.—S. O. Waife

DIABETES ABROAD

The following series of papers depict some of the problems with which the physician is confronted in the practical dietary management of diabetes in various European countries and in Canada.

The Social Problems Posed by the Diet in Diabetes Mellitus. R. Boulin. *Méd. et Hygiène* 11(250): 337, 1953.

In this paper Boulin discusses the practical dietary management of the diabetic in France today. The "social problem" of the diabetic diet arises only in cases in which treatment includes a weighed regimen —and all French specialists prescribe such a regimen. (Diabetics treated by specialists are, however, a minority in France.)

When the French diabetic lives at home, the problem of keeping on the diet is a financial one, since the cost of adherence to it is beyond the means of most patients. The result is that French diabetics have recourse to higher dosés of insulin than they would require if a proper diet were feasible (they are reimbursed for insulin by the Social Security system). Special nonprofit food stores, where the physician's "prescription" for food would be honored are suggested as the appropriate solution to this problem.

French diabetics who must take one or all of their meals in restaurants are faced with another unsolved problem. The opening of special restaurants for diabetics is unlikely, since their ability to make a profit is doubtful. If enough restaurants would augment their regular bill of fare with a special "diabetic menu," this problem would be alleviated to a certain extent.

For diabetics living a communal life—as in schools, convents, seminaries, etc.—no solution is apparent.

As for the care of hospitalized diabetics, those treated in services directed by diabetes specialists are very few in comparison to the total number of hospitalized diabetics. Few services are provided with special diet kitchens, but the weighing of food seems to be correct in all services, provided there is strict supervision. Diets are usually, but not always, varied; most physicians prescribe such diets; those using a "standard" diet (personal with each physician) are a minority. Families are forbidden to bring food to patients, but often succeed in doing so. About 70 per cent of hospitalized diabetics follow the diet strictly.

Diabetics in convalescent homes, clinics, etc., which specialize in such cases present no problem, but more dieticians are needed for diabetics admitted to such institutions for postoperative recuperation; and it has been suggested that diabetics with tuberculosis be grouped separately in sanatoria for better dietary control.

Finally, the matter of food products advertised and sold as suitable for diabetics is discussed. Patients, reassured by the label, may be misled into believing they may eat inordinate amounts of these foods. The products are not always analyzed; the carbohydrate content of some is scarcely less than in normal products; and some contain carbohydrates of doubtful assimilability. All these products should be strictly controlled, and should not be labeled "for diabetics" until they have been investigated and certified by a national commission of specialists.—C.-J. Howell

Social Dietetic Prophylaxis of Diabetes. E. Arias Vallejo. *Méd. et Hygiène* 11(250): 338, 1953.

The problem of whether or not it is possible to prevent diabetes mellitus is a difficult one to solve. Its hereditary character is universally recognized, but its eventual appearance may be favored or accelerated by certain exogenous factors. Perhaps the most important of these is nutrition. According to the author the normal diet may exhaust the endocrine function of the pancreas in an individual predisposed to diabetes. It is here that the possibility of prophylaxis appears. Since obesity is admittedly prodromal to many cases of diabetes, the prophylactic regimen must have as its object the reduction of weight when obesity exists and the prevention of obesity where it has not yet appeared. Such a regimen must furnish approximately 2400 calories (3000 for more active persons) and should be high in protein, low in carbohydrates and fats. For the 2500 calorie regimen, 90 Gm. of protein are recommended (100 Gm. for 3000 calories). Fats should represent approximately 20 per cent of the total calories (40–50 Gm. per day); carbohydrates should make up the rest: 420–540 Gm. The principal object of this diet is to maintain the *ideal weight* of the individual.

The selection of patients to be placed on such a regimen may be determined by logical considerations, such as the hereditary factor. In Arias' opinion every child of a diabetic, especially if he or one of his parents presents the constitutional type of anterior hyperpituitarism, will probably suffer from diabetes in the course of his lifetime. This probability becomes almost a certitude when both parents are diabetics. Furthermore, the presence of a *prediabetic syndrome* will naturally constitute an indication for the above regimen. This syndrome is characterized clinically by the frequent appearance of certain disorders, such as staphylococcus infections and neuritides, and by the results of certain laboratory tests (intermittent glycosuria; slight basal hyperglycemia; prolonged postprandial hyperglycemic curve; hyperglycemic response to the two-dose glucose tolerance test; decrease of the arteriovenous glucose difference).

Other indications for the diet are persons with "suspicious" conditions: The author includes under this designation pregnant women; patients with "pancreatropic" disease (hepatitis, varicella, mumps); and persons—confectioners, for example—whose habitual diet is over-rich in sweets.

The principal agent in such a prophylactic program must be the family physician, although state and private organizations can participate through "propaganda."—C.-J. Howell

Nutrition Education, Social Problem in the Prevention and Treatment of Diabetes. J. Lederer. *Méd. et Hygiène* 11(250): 337, 1953.

Since it has long been known that obesity, if not the determining cause of diabetes, at least favors its appearance, the importance of educating the public is obvious. The author treats all his diabetics as *cases of obesity*, stressing the absolute necessity of weight reduction. On the basis of physical activity, he prescribes either a 1250-calorie or a 1500-calorie regimen. Co-operative patients find no difficulty in following these diets once they are on them—but it is not easy to get most patients to undertake them. Of 401 diabetics treated, only 64 lost 5 Kg. or more. The lack of will power and the *gourmandise* of the patient constitutes one difficulty; the ignorance of many as to the value of foods is another.

Practical diabetes prevention involves, above all, the education of the whole public on the implications of obesity, food values, and especially the dangers of overindulgence in sweets. While the population as a whole must be reached in this campaign, it is particularly important that the descendants of diabetics be made aware of these facts. Not only sweets, but fats as well, must be restricted in the diabetic (and "prediabetic") diet, both to avoid arteriosclerosis and to insure better regulation of carbohydrate metabolism. "Special" foods are not necessary; the well-informed patient can adhere to a diabetic regimen without recourse to these costly products.—C.-J. Howell

Considerations and Practical Studies on Dietary Cholesterol in Diabetes and Obesity. R. Lachance. *Gaz. méd. France* 60: 37, 1953.

The author defends the closest possible adherence to the normal diet in the treatment of nutritional disturbances of all kinds, and presents figures on 400 patients in a Canadian diabetes and nutrition service. All were hospitalized for a nutritional disturbance of some sort. Obese and nonobese diabetic and nondiabetic obese subjects were studied in detail.

Without regard to age, sex, or individual metabolic state, 125 of 400 admission blood cholesterols were normal (30%); 90 (22.5%) slightly above normal; 70 (17.5%) quite high; and only 15 (3.75%) below normal. Seventy per cent of the 400 patients were diabetics; 25% were obese; 5% were underweight. The diabetics generally had a relatively high cholesteremia (10% normal; 60% slightly elevated; 30% elevated). Obese subjects had very high blood cholesterol levels. Among patients with rather high cholesterol levels, women tended to have the highest (average of 10% more than the men). The highest levels were found in the age group 40–55. There was a seasonal variation in blood cholesterol level, which was found to be higher in the period Sept.–April than in May–Sept.

Diets for overweight subjects were established on a reducing and sedentary basis at 1200 to 2400 calories. Lipids supplied 405–810 cal.; proteins were furnished in the amount of 1 to 1.5 Gm./Kg.; carbohydrates made up the remainder.

Upon discharge, variations in blood cholesterol level were as follows: unchanged—5%; higher—10%; lower—85%. Decreases occurred in the following proportions in the various groups: mild diabetics—10.5%; severe diabetics—12.5%; obese—14.5%; diabetics with obesity—12.5%.

While the author makes no claim that the "normal diet" is a panacea for all nutritional disorders, the successful management of obesity and diabetes on this program is interesting.—C.-J. Howell

Diabetes Mellitus, a Disease of the Well-to-do. A. Fleisch. *Gaz. méd. France* 60: 31, 1953.

During the last world war, Swiss food was rationed, and diabetics could get extra quotas of scarce meat and fat by declaring themselves and submitting a confirmatory medical certificate. It was therefore possible, for the first time, to get statistical evidence on the frequency of diabetes in Switzerland. The author found a considerable variation in regional incidence: less than 2 per 10,000 in some cantons, over 10 per 10,000 in others. Curious to see whether any revealing correlations could be discovered which might explain these regional differences, he made a study of various canton statistics. He found a close correlation only between diabetes and the amount of "emergency tax" paid (which, in turn, was a reflection of prosperity). The coefficient of correlation was 0.918 which is extremely significant. The problem remained: was wealth *per se* the "significant" factor, or was this some other circumstance connected with wealth? The author then considered the factor of occupation, since, as he engagingly observes: "Large revenues are not earned by physical labor but by intellectual labor." Further calculations did indeed reveal that not only was diabetes more frequent in the more prosperous cantons, but also that the more intellectual workers there were in a canton, the more frequent was the disease, and the more agricultural workers in a canton, the fewer the number of diabetics. After working out the correlations for these factors (and they were not as significant as the first), and taking into consideration other matters (such as the possibility that fewer farmers might have been diagnosed, and that fewer farmers might have revealed themselves as diabetics by asking for extra rations, since they could more easily supply themselves), the coefficient of correlation for tax-diabetes remained highly significant at 0.811. The author feels, therefore, that "statistics prove" the correctness of his paper's title.

If any lurking doubt remains in Prof. Fleisch's mind as to whether high life or high thought is involved in the development of diabetes, we invite him to extend

his researches to the United States, where he will have no difficulty in finding large numbers of intellectual workers with low incomes and equally large numbers of physical laborers with high incomes.—C.-J. HOWELL

Frequency of Diabetes Mellitus in the Netherlands. F. S. P. van Buchen. *Méd. et Hygiène* 11(250): 339, 1953.

Investigations of the incidence of diabetes in several parts of the Netherlands between 1940 and 1943 reveal a variation of from 2.36 to 6 per 1000 inhabitants.

Diabetes mortality rose gradually from 1903 to 1937, coincident to a decline in overall mortality. Since 1938, diabetes mortality has fallen, and in 1951 was 1.14 per cent compared to 1.90 per cent in 1937.

Factors contributing to the decline may include the altered age pattern of the population, the prolongation of the life of diabetics, a more abundant diet (fat), and a decrease in mortality in the Netherlands since 1938.

Evidence of a correlation between frequency of diabetes, an abundant dietary intake, and obesity is cited, as is the high frequency of atherosclerosis among diabetics and its possible relation to cholesterol and/or fat in the diet.

The author recommends a regimen which, while fully adequate to the body's needs, will maintain it at slightly *less* than normal weight. To insure normal development of young diabetics, carbohydrates should be given in the amount of 200–250 Gm. per day.

It is important to prevent permanent hyperglycemia, with its ultimate unfavorable influence on carbohydrate tolerance. Hyperglycemia, while it doubtless represents an adaptation of the organism favoring glucose utilization, leads in the end to serious consequences. It may also increase the probability of cardiovascular complications.

The so-called "free diet," which has as its aim the limiting of glycosuria, is accompanied by a slightly higher blood glucose level. Hence, in the light of evidence on the dangers of permanent hyperglycemia, the author advises a somewhat stricter regimen.—C.-J. HOWELL

NUTRITION EDUCATION IN THE UNITED KINGDOM

Nutritionists in America will be interested in the following abstracts of reports appearing in the Proceedings of the British Nutrition Society.

1. **The Education of the Schoolchild in Nutrition.** E. M. Hale. *Proc. Brit. Nutrition Soc.* 12: 166, 1953.

The nutritional education of the schoolchild is designed to provide him with an understanding of what constitutes a state of good nutrition, the desirability of such a state, and his responsibilities in this matter. A consideration of the needs of the community may develop later. Little if any direct teaching in the subject can be given in the Nursery and Infant School, but the routine is so organized that valuable habits are formed through the children's daily activities, and their interest may be elicited by judicious selection of topics for consideration and discussion.

The education of schoolchildren in nutrition may proceed throughout school life. Attempts are made at all stages to present by implication and by direct teaching such material as the pupil can understand and appreciate. How much can be done depends on the aptitude of the pupils and the facilities available, the aim being always to provide as much knowledge as the pupil can safely assimilate and is likely to require in order to maintain good health and, when appropriate, to prepare for further study at a higher level.—B. SURE

2. **The Education of Housecraft Teachers in Nutrition (England and Wales).** E.R. House. *Proc. Brit. Nutrition Soc.* 12: 170, 1953.

Girls who are intending to make a career as domestic science teachers have a wide range of colleges from which to choose for their training. Such training colleges offer a varied 3-year course. Some have a definite bias toward one or another branch of this wide subject, but all build their work round the home and the needs of various members of the household. Since good nutrition is a fundamental essential of family well-being, the study of nutrition education is common to all colleges. The previous preparation of students on entry to college varies considerably, but the nutrition course during their training follows four lines, all leading to the practice of good nutritional habits based on scientific knowledge and to the ability to teach this to others. Though the student-in-training has ample help with her nutrition education, further stimulus and guidance are needed for the practising teachers, who all too often find it difficult to keep their nutrition knowledge up to date.—B. SURE

3. **The Education of Medical Students in Nutrition.** S. J. Cowell. *Proc. Brit. Nutrition Soc.* 12: 173, 1953.

There are two distinct aspects of nutrition of importance to the medical practitioner. There is first the knowledge of general principles, which on the one hand will enable him to secure for the individuals and families in his care the perfection of development in early years that depends on right feeding, and, on the other hand, will furnish him with a potent means of maintaining his older patients in vigorous health. Secondly, the medical man requires a knowledge of how normal diets can be modified, so that they may make their fullest contribution to the treatment of his individual patients when they fall sick. Clinical teachers then should be available with an up-to-date knowledge of nutrition in health and disease. They

should be as familiar with the chemical composition of common foods as with the pharmacological make-up of common drugs. They must also be capable of appraising claims by the distributors of new special foods and preparations of vitamins as critically as they assess the advertised virtues of new drugs and medical appliances.—B. SURE

4. Nutrition Education in the Army. F. S. Leben. *Proc. Brit. Nutrition Soc.* 12: 181, 1953.

Efficient nutrition in the army is of great importance for three reasons. It helps maintain good health among the troops; it helps keep up the standard of physical efficiency the army requires; and it helps maintain morale. The type of nutrition education provided in the army is of an essentially practical nature. Roughly speaking, there are four levels at which nutrition is taught: to medical officers and nursing officers; to officers and men of the Army Catering Corps; to various other specialist ranks of the R.A.M.C. and Q.A.R.A.N.C., such as nursing orderlies and hygiene assistants; and to regimental officers and other ranks.

The Royal Army Medical College organizes courses mainly for various medical officers, and nutrition is included in all the courses. Short introductory courses are given to national service medical officers on entry into the army, and longer instruction is given to service medical officers after about 10 years of service. Both these courses include two lectures on nutrition, which cover much ground in a short time. The emphasis of these lectures is on the calorie requirements of the soldier and on demonstrating how to draw up a ration scale. Food hygiene is dealt with in separate lectures. A special course is given for officers of the Royal Army Service Corps, whose duties include the handling of the army food supplies. All medical officers attending courses at the College are provided with a set of nutrition notes, which are continually brought up to date. They contain basic information on nutritional principles, as well as information relevant to nutrition in the army, e.g., nutritive value of various army ration scales.

The College museum includes a nutrition exhibit illustrating the principles of a balanced diet and how to apply them in the army. Exhibits of various army ration packs are included. From time to time an Army Health specialist on a course may be selected to reorganize and bring up to date the nutrition section of the museum as part of his training.—B. SURE

5. The Royal Sanitary Institute Certificate in Nutrition. H. E. Magee. *Proc. Brit. Nutrition Soc.* 12: 193, 1953.

Toward the end of World War II it became evident that courses in elementary nutrition and dietetics were needed for people who had been engaged in community feeding, as in industrial and other canteens, in hospitals and schools, and in residential institutions. It soon became clear that the demand for such courses would increase with the end of the war. The anticipation proved to be true, and large numbers of demobilized men and women, who had been working at catering, cooking, or serving food in messes, hospitals and canteens, stated that they would welcome instruction of a practical nature in nutrition and dietetics. Technical schools and institutes were obviously the most desirable places for their purpose, and inquiries made in some of them showed that they would welcome the chance to give such courses provided it would lead, after a suitable examination, to a certificate or diploma conferred by a responsible and authoritative organization. The Royal Sanitary Institute expressed its willingness in 1945 to conduct examinations in several centers throughout the country and to award an official certificate of the Institute to successful candidates.

The course of training approved requires not less than 120 hours of theoretical and practical instruction, either whole or part time, to be completed in not more than one year. The instruction is to be given in the form of lectures, demonstrations, discussions, and practical work in the laboratory and kitchen; visits to selected institutions, such as hotels and hospitals, are recommended. The curriculum covers the basic principles of nutrition and their application, the composition of food, its digestion, absorption, and metabolism, nutritional requirements and food in relation to physique and health, the effects of cooking on food, principles of catering, construction of menus, the use of food tables, and the planning of balanced meals for various types of persons. Instruction is given also in the modifications of diet required for persons suffering from chronic gastric disease, the effects of preservation and storage on the nutritive value of foods, and the cost of essential nutrients and its effect on the composition of family diets.—B. SURE

ITEMS OF GENERAL INTEREST

Changes in the Mean Stature and Weight of British Children over the Past Seventy Years. E. M. B. Clements. *Brit. Med. J.* 1: 897, 1953.

The paper presents a comparison of heights and weights of British children age 5 to 13 years since 1883. The data used were drawn from nine surveys covering the following four periods: late 19th century, the First World War, the interwar years, and the Second World War. The data were sufficiently detailed to allow standardization of methods of calculating age, weight, and stature, and provided information enough to determine the social class of the individuals. Although some of the data were drawn from different urban areas at different time periods, it was possible to show that in one period there was no difference between the heights and weights of children in London, Glasgow, and Birmingham.

The data show that the average stature and weight increased 2.5 to 3.5 inches and from 4 to 11 pounds between 1880 and 1947. An average 6-year-old child in 1947 was found to be approximately the same size as one 7.5 years in 1880. The increase in anthropometric measurements was greatest in the lower economic groups. The difference in size of children between upper and lower economic groups which was marked in 1880 is reported to have all but disappeared. The rate of increase in growth was interrupted during both the First and Second World Wars.—H. L. TAYLOR

Medical Progress, Food Poisoning. K. F. Meyer. *New England J. Med.* 249: 765, 1953.

The writer has presented an authoritative review on the prevalence, etiology, and epidemiology of food poisoning.

Much confusion exists concerning the exact nature of food poisoning. This has been due in part to a lack of accurate information about the epidemiology and more specifically about the bacteriology of the illness.

Data concerning prevalence is incomplete. Outbreaks are reported to public health officials in only ten states. This makes it difficult to have an exact idea as to the absolute prevalence in the United States. In about one-half of the reported cases the etiologic bacterial agent was not determined.

The following micro-organisms are generally considered the causes of outbreaks: Staphylococci, salmonella, streptococci, *Esch. coli* and *paracoli*, shigella, *Aerobacter aerogenes* group, *Cl. perfringens* (*welchii*) and *botulinum*. In the United States staphylococcus was found to be the principal causative agent, with salmonella running second.

Staphylococcal enterotoxic gastroenteritis, its clinical manifestations, bacteriology, and epidemiology are discussed.—M. W. BATES

Effects of Diet on Urinary Excretion of Histamine. R. G. Mitchell and C. F. Code. *J. Appl. Physiol.* 6: 387 1954.

When healthy adults were fasted the urinary excretion of free and conjugated histamine was reduced. Free histamine fell to a relatively constant fixed amount during this period. It was suggested that this may indicate total histamine metabolism in the absence of digestion. Bread and milk diets did not change urinary free histamine when compared to control basal values. Urinary excretion of free and conjugated histamine was increased by a meat diet. Excretory values of conjugated histamine were quite labile.

If histamine were taken by mouth in conjunction with a meal of milk, bread, and butter, the urinary excretion of free histamine was increased. If histamine or the meal were taken separately, there was no effect.—M. J. OPPENHEIMER

Serum Phospholipid and Rheumatic Fever. A. D. Wallis and E. Viergiver. *Am. J. Med. Sc.* 227: 171, 1954.

The average serum phospholipid levels in childhood were found to be lower than in adults. The effectiveness of the serum inhibitor of Streptolysin S depends in part on phospholipid which is lowest at the usual time of onset of rheumatic fever. The importance of this relationship lies in the suspicion that Streptolysin S may represent a cause of this disease. In studying 178 patients with inactive rheumatic heart disease, serum phospholipid was found to be lower than the normal average for the age. Dietary histories showed that the ingestion of eggs was low in a high percentage of patients with rheumatic disease. This was considered significant because of the importance of eggs as a source of choline used in phospholipid formation. It is suggested that rheumatic fever is produced when a hemolytic streptococcal infection produces more Streptolysin S than the natural phospholipid-derived serum inhibitor is able to neutralize.—C. R. SHUMAN

Dietary Eggs and Rheumatic Fever. A. D. Wallis. *Am. J. Med. Sc.* 277: 167, 1954.

The author believes that serum phospholipid is a component of the natural inhibitor of the streptococcal hemolysin known as Streptolysin S. Because eggs are the richest dietary source of dietary choline, which may be important in the synthesis of phospholipid, dietary surveys with regard to eggs were taken in 184 patients with rheumatic heart disease and 1380 normal persons. By the recall method, the author feels that 40 per cent of the cardiac patients ate few eggs in childhood, as compared with 16 per cent of the control subjects. A history of the restriction of eggs in childhood was given by 49 per cent of those requiring digitalis for the control of heart disease and by 51 per cent of those who had had three or more acute episodes of rheumatic fever. Individual differences in choline intake and requirements may be of significance in determining the susceptibility to rheumatic fever.—C. R. SHUMAN

Nutritional Value of Canned Foods. H. Cheftel. *Méd. et. Hygiène* 11 (250): 335, 1953.

The loss of vitamins and essential amino acids is no greater in canning processes than in ordinary home cooking. Heat sterilization does not affect protein quality. Of the vitamins, ascorbic acid is retained when heating proceeds without oxidation, and only thiamine is threatened by heat alone. In general, however, the losses are less than in the case of "fresh" home-cooked foods, and it is estimated that 70 to 90 per cent of the original vitamin value of the food is retained after canning.

Canned foods may therefore safely be used in any diet, and their value is especially great in certain regimens where their variety, taste appeal, and con-

venience can facilitate adherence to low calorie, low cellulose, low sodium, and other therapeutic diets. The use of canned baby foods may be helpful in maintaining adequate nutrition in elderly persons as well as infants. A wise selection from ordinary canned foods will be sufficient in many cases, but in others, specially prepared "diet" foods may be necessary. In all such cases, the actual composition of canned goods labeled as suitable for "saltless" or "sugarless" diets must be rigidly controlled. The technical problems involved in preserving foods without salt or sweetening are considerable, and great care must be exercised by the producer if contamination by the usual preservatives is to be avoided. For example, equipment (vats, conveyor belts, etc.) which has been in contact with salt or sweet foods must be scrupulously cleaned before "special" foods are run through, and some of the customary methods of cleaning and preserving foods before canning (such as immersion in brine) must be avoided. Even plain water must be checked carefully, since in certain regions its sodium content is unusually high.

A greater knowledge of nutritional and medical problems on the part of the producer, and a greater interest on the part of physicians and nutritionists in the possibilities and problems of processing special foods would extend still further the usefulness of canned goods in the normal and therapeutic diet.—C.-J. HOWELL

Vasoconstriction in the Cheek Pouch of the Hamster Following Treatment with Cortisone. L. C. Wyman, G. P. Fulton, M. H. Shulman, and L. L. Smith. *Am. J. Physiol.* 176: 335 1954.

Cortisone acetate produces vasoconstriction in cheek pouch vessels which appears after a delay of 9 days. The time course of appearance and disappearance was the same for single and repeated doses. Blood pressures were normal and there was no change in mesoappendix vessels at the time at which the cheek pouch vessels were constricted.—M. J. OPPENHEIMER

Influence of Lactose on the Transglycosidation of Sphingosine Base in the Rat Brain. D. P. Sadhu. *Am. J. Physiol.* 175: 283, 1953.

In these experiments rats were fed whole and skim milk. They were examined for changes in cerebroside, sphingomyelin, phospholipid, and sphingosine bases in brain. Skim milk fed rats showed an increase of galactocerebroside and a fall in sphingomyelin. Liver fat was decreased. These same rats on skim milk showed a lessened dehydrogenase activity in liver and kidney. However, the same activity was increased in intestine of these rats.—M. J. OPPENHEIMER